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Acupuncture for neuropathic pain in adults (Review)

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[Intervention Review]

Acupuncture for neuropathic pain in adults

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ABSTRACT

Background

Neuropathic pain may be caused by nerve damage, and is often followed by changes to the central nervous system. Uncertainty remains regarding the effectiveness and safety of acupuncture treatments for neuropathic pain, despite a number of clinical trials being undertaken.

Objectives

To assess the analgesic efficacy and adverse events of acupuncture treatments for chronic neuropathic pain in adults.

Search methods

We searched CENTRAL, MEDLINE, Embase, four Chinese databases, ClinicalTrials.gov and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) on 14 February 2017. We also cross checked the reference lists of included studies.

Selection criteria

Randomised controlled trials (RCTs) with treatment duration of eight weeks or longer comparing acupuncture (either given alone or in combination with other therapies) with sham acupuncture, other active therapies, or treatment as usual, for neuropathic pain in adults. We searched for studies of acupuncture based on needle insertion and stimulation of somatic tissues for therapeutic purposes, and we excluded other methods of stimulating acupuncture points without needle insertion. We searched for studies of manual acupuncture, electroacupuncture or other acupuncture techniques used in clinical practice (such as warm needling, fire needling, etc).

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. The primary outcomes were pain intensity and pain relief. The secondary outcomes were any pain-related outcome indicating some improvement, withdrawals, participants experiencing any adverse event, serious adverse events and quality of life. For dichotomous outcomes, we calculated risk ratio (RR) with 95% confidence intervals (CI), and for continuous outcomes we calculated the mean difference (MD) with 95% CI. We also calculated number needed to treat for an additional beneficial outcome (NNTB) where possible. We combined all data using a random-effects model and assessed the quality of evidence using GRADE to generate 'Summary of findings' tables.

Main results

We included six studies involving 462 participants with chronic peripheral neuropathic pain (442 completers (251 male), mean ages 52 to 63 years). The included studies recruited 403 participants from China and 59 from the UK. Most studies included a small sample size (fewer than 50 participants per treatment arm) and all studies were at high risk of bias for blinding of participants and personnel. Most studies had unclear risk of bias for sequence generation (four out of six studies), allocation concealment (five out of six) and selective reporting (all included studies). All studies investigated manual acupuncture, and we did not identify any study comparing acupuncture with treatment as usual, nor any study investigating other acupuncture techniques (such as electroacupuncture, warm needling, fire needling).

One study compared acupuncture with sham acupuncture. We are uncertain if there is any difference between the two interventions on reducing pain intensity (n = 45; MD -0.4, 95% CI -1.83 to 1.03, very low-quality evidence), and neither group achieved 'no worse than mild pain' (visual analogue scale (VAS, 0-10) average score was 5.8 and 6.2 respectively in the acupuncture and sham acupuncture groups, where 0 = no pain). There was limited data on quality of life, which showed no clear difference between groups. Evidence was not available on pain relief, adverse events or other pre-defined secondary outcomes for this comparison.

Three studies compared acupuncture alone versus other therapies (mecobalamin combined with nimodipine, and inositol). Acupuncture may reduce the risk of 'no clinical response' to pain than other therapies (n = 209; RR 0.25, 95% CI 0.12 to 0.51), however, evidence was not available for pain intensity, pain relief, adverse events or any of the other secondary outcomes.

Two studies compared acupuncture combined with other active therapies (mecobalamin, and Xiaoke bitong capsule) versus other active therapies used alone. We found that the acupuncture combination group had a lower VAS score for pain intensity (n = 104; MD -1.02, 95% CI -1.09 to -0.95) and improved quality of life (n = 104; MD -2.19, 95% CI -2.39 to -1.99), than those receiving other therapy alone. However, the average VAS score of the acupuncture and control groups was 3.23 and 4.25 respectively, indicating neither group achieved 'no worse than mild pain'. Furthermore, this evidence was from a single study with high risk of bias and a very small sample size. There was no evidence on pain relief and we identified no clear differences between groups on other parameters, including 'no clinical response' to pain and withdrawals. There was no evidence on adverse events.

The overall quality of evidence is very low due to study limitations (high risk of performance, detection, and attrition bias, and high risk of bias confounded by small study size) or imprecision. We have limited confidence in the effect estimate and the true effect is likely to be substantially different from the estimated effect.

Authors' conclusions

Due to the limited data available, there is insufficient evidence to support or refute the use of acupuncture for neuropathic pain in general, or for any specific neuropathic pain condition when compared with sham acupuncture or other active therapies. Five studies are still ongoing and seven studies are awaiting classification due to the unclear treatment duration, and the results of these studies may influence the current findings.

PLAIN LANGUAGE SUMMARY

Acupuncture for neuropathic pain in adults

Review question

Is acupuncture safe and effective in the treatment of chronic neuropathic pain in adults?

Background

Neuropathic pain is a complex, chronic pain caused by damaged nerves. It is different from pain messages that are carried along healthy nerves from damaged tissue (for example, a fall or cut, or arthritic knee). Approximately 7% to 10% of the general population have neuropathic pain. Acupuncture is a traditional Chinese medicine (TCM) technique of treating disease by inserting needles into the skin, or the tissues below.

In this review, we were interested in whether acupuncture could relieve pain, improve quality of life, and cause fewer side effects than other treatment options, for adults with neuropathic pain. We looked for studies comparing acupuncture with sham acupuncture (sham acupuncture involves using a blunt needle that slides into the handle rather than penetrating the skin or tissues below). We also looked for studies comparing acupuncture with treatment as usual, or with other active therapies (such as mecobalamin, nimodipine, inositol, and Xiaoke bitong capsule).

Study characteristics

We conducted a search for relevant clinical trials in February 2017. We included six studies of manual acupuncture: one compared acupuncture with sham acupuncture; three investigated acupuncture combined with other active treatments compared with other active treatments alone; two compared acupuncture alone compared with other active treatments. The six studies involved 462 adults with chronic peripheral neuropathic pain. The participants were 52 to 63 years of age, on average. They received treatment for eight weeks or

more. We did not find any study comparing acupuncture with treatment as usual, nor any study of other acupuncture techniques (such as electroacupuncture, warm needling, fire needling).

Key results and quality of evidence

We are uncertain about the beneficial effects of manual acupuncture on pain intensity, pain relief and quality of life when compared to sham acupuncture or other therapies (such as mecobalamin, nimodipine, inositol, and Xiaoke bitong capsule). There is a lack of evidence on the potential harms (side effects) of acupuncture.

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. The quality of the evidence in this review is very low, mostly due to problems in the way the studies were conducted (such as the participants were not blinded to their treatment, or more participants in the sham acupuncture group left the study early). The studies also included a small number of participants. Moreover, these findings only apply to peripheral neuropathic pain in older adults.

Overall, we do not have sufficient evidence to support or refute the use of acupuncture in treating neuropathic pain.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Acupuncture versus sham acupuncture for neuropathic pain in adults

Acupuncture versus sham acupuncture for neuropathic pain in adults

Patient or population: adults with neuropathic pain
Settings: hospital
Intervention: acupuncture

Comparison: sham acupuncture

Outcomes	Sham acupuncture	Acupuncture	Relative effect MD (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain intensity VAS (0-10, lower score = less pain) Follow-up: 10 weeks	Mean 6.2	Mean 5.8	The mean participant-reported pain intensity in the intervention group was **0.40 lower** (1.83 lower to 1.03 higher)	45 (1 study)[a] in which 59 participants began treatment)	⊕⊖⊖⊖ **very low**[b,c]	Acupuncture has no clinical significant beneficial effects on pain intensity compared to sham acupuncture.
Participant-reported pain relief substantial (at least 50% pain relief over baseline)	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.
Participants experiencing any serious adverse event	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.

Quality of life SF-36 bodily pain score (0-100, lower score = more disability) Follow-up: 10 weeks	Mean 27.7	Mean 37.7	The mean bodily pain component of quality of life in the intervention groups was **10 higher** (3.13 lower to 2313 higher)	45 (1 study)	⊕⊖⊖⊖ **very low**[b,c]	Acupuncture has no beneficial effects on bodily pain compared to sham acupuncture.

CI: confidence interval; **MD**: mean difference; **SF-36:** Short Form (36) Health Survey (SF-36); **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Garrow 2014 recruited 59 participants initially; there were 14 withdrawals and only the 45 participants that completed treatment were included in the study's final results.
[b]Downgraded twice for study limitations (risk of bias) due to high risk of performance and attrition bias; high risk of bias confounded by small size of study.
[c]Downgraded once for imprecision due to wide 95% CI (the wide CIs were usually induced by small sample size and low incidence of events).

Summary of findings 2. Acupuncture versus treatment as usual for neuropathic pain in adults

Acupuncture versus treatment as usual for neuropathic pain in adults

Patient or population: adults with neuropathic pain
Settings: hospital
Intervention: acupuncture

Comparison: treatment as usual

Outcomes	Sham acupuncture	Acupuncture	Relative effect (Not applicable)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain intensity	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.

Participant-reported pain relief	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.
Participants experiencing any serious adverse event	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.
Quality of life	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 3. Acupuncture versus other active therapy for neuropathic pain in adults

Acupuncture versus other active therapy for neuropathic pain in adults

Patient or population: adults with neuropathic pain
Settings: hospital
Intervention: acupuncture

Comparison: other active therapy

Outcomes	Sham acupuncture	Acupuncture	Relative effect (Not applicable)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain intensity	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.
Participant-reported pain relief	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.

Participants experiencing any serious adverse event	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.
Quality of life	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 4. Acupuncture combined with other active therapy versus other active therapy for neuropathic pain in adults

Acupuncture combined with other active therapy versus other active therapy for neuropathic pain in adults

Patient or population: adults with neuropathic pain
Settings: hospital
Intervention: acupuncture combined with other active therapy

Comparison: other active therapy alone

Outcomes	Other active therapy	Acupuncture combined with other active therapy	Relative effect (MD (95% CI))	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Participant-reported pain intensity VAS (0-10, lower score = less pain) Follow-up: 84 days	Mean 4.25	Mean 3.23	The mean participant-reported pain intensity in the intervention groups was 1.02**lower** (1.09 lower to 0.95 lower)	104 (1 study)	⊕⊖⊖⊖ **very low**[a.b]	Acupuncture combined other active therapy has no clinical significant beneficial effects on pain intensity compared to other active therapy alone.

Participant-reported pain relief substantial (at least 50% pain relief over baseline)	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.
Participants experiencing any serious adverse event	-	-	-	-	-	No studies reported this outcome so no evidence to support or refute benefits of intervention.
Quality of life FACT/the GOG-Ntx questionnaire scores (0 - 100, lower score = better) Follow-up: 84 days	Mean 35.17	Mean 32.98	The mean bodily pain component of quality of life in the intervention groups was 2.19**lower** (2.39 lower to 1.99 lower)	104 (1 study)	⊕⊕⊖⊖ **low**[a]	Acupuncture combined other active therapy improved the quality of life compared to other active therapy alone.

CI: confidence interval; **FACT/the GOG-Ntx:** Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity; **MD**: mean difference; **VAS:** Visual Analogue Scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice for study limitations (risk of bias) due to high risk of performance and detection bias.
[b]Downgraded once for imprecision due to wide 95% CI (the wide CIs were usually induced by small sample size and low incidence of events).

BACKGROUND

We based the methods of this review on a template used to review drugs to relieve neuropathic pain. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1).

Description of the condition

The 2011 International Association for the Study of Pain defined neuropathic pain as "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011), based on a previously agreed definition (Treede 2008). Neuropathic pain may be caused by nerve damage, and is often followed by changes to the central nervous system (Moisset 2007). Pain can be severe and may be present for months or years. The origin of pain is complex (Apkarian 2011; Tracey 2011), occurring in approximately between 6.9% and 10% of the population worldwide (Van Hecke 2014). Many people with neuropathic pain conditions are significantly disabled and experience moderate or severe pain for many years.

Neuropathic pain is usually classified according to the cause of nerve injury. The common causes of neuropathic pain include painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN), amputation (stump and phantom limb pain), neuropathic pain after surgery or trauma, trigeminal neuralgia, stroke or spinal cord injury, and HIV infection. Neuropathic pain is also divided into peripheral neuropathic pain, central neuropathic pain (brain and spinal cord), or mixed (peripheral and central) neuropathic pain. Subsequently, there is an ongoing debate regarding the efficacy of different drugs for central versus peripheral neuropathic pain (Finnerup 2015).

Systematic reviews have reported that the overall prevalence of neuropathic pain in the general population is between 7% and 10% (Moore 2014b; Van Hecke 2014). In individual countries, prevalence rates of 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), and up to 8% in the UK (Torrance 2006) have been reported. Reports regarding the occurrence of some forms of neuropathic pain, such as PDN and post-surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008).

The small number of cases of neuropathic pain has resulted in varying estimates of incidence between individual studies. Between 2002 and 2005 in the UK (per 100,000 person-year observation) there were 28 incidences of PHN recorded (95% confidence interval (CI) 27 to 30), 27 cases of trigeminal neuralgia (95% CI 26 to 29), 0.8 for phantom limb pain (95% CI 0.6 to 1.1), and 21 incidences of PDN (95% CI 20 to 22) (Hall 2008). Other studies estimate the incidence of trigeminal neuralgia at 4 per 100,000 (Katusic 1991; Rappaport 1994), and 12.6 per 100,000 (Koopman 2009), with estimates of 3.9 per 100,000 for PHN in the Netherlands (Koopman 2009). One systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as PDN, are more common than other neuropathic pain conditions, with prevalence rates up to 400 per 100,000 (McQuay 2007).

Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical or cognitive interventions, or both. Conventional analgesics, such as paracetamol and nonsteroidal anti-inflammatory drugs, are not thought to be effective, but are frequently used (Di Franco 2010; Vo 2009). Some people may derive some benefit from a topical lidocaine patch or low-concentration topical capsaicin, although evidence about the benefits of these interventions is unproven (Derry 2012; Derry 2014). High-concentration topical capsaicin may benefit some people with PHN (Derry 2013), and treatment using so-called 'unconventional analgesics', such as antidepressants (duloxetine and amitriptyline) (Lunn 2014; Moore 2012a; Sultan 2008), or antiepileptics (gabapentin or pregabalin) (Moore 2009; Moore 2011a; Wiffen 2013), are often prescribed.

One overview of treatment guidelines pointed out some general similarities between recommendations, but guidelines overall remain inconsistent (O'Connor 2009). The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013a) is small, and is generally only 10% to 25% more when compared with placebo. The numbers needed to treat for an additional beneficial outcome are usually between 4 and 10 (Kalso 2013; Moore 2013b). Therefore, neuropathic pain is not particularly different from other chronic pain conditions, with only a small proportion of trial participants experiencing a good response to treatment (Moore 2013b).

Chronic pain conditions comprised five of the 11 top-ranking global conditions for years lived with disability in 2010 (Vos 2012), and are responsible for a considerable reduction in quality of life, loss of employment, and increased healthcare costs (Moore 2014b).

Description of the intervention

Acupuncture is sought and offered as a treatment for pain in many societies (Macpherson 2004; Zhao 2011). Acupuncture is defined as needle insertion and stimulation of somatic tissues for therapeutic purposes. Acupuncture points (or acupoints) are described in anatomical regions but have no anatomical or physiological substrate to define them. Inserting needles at acupuncture points often involves the targeting of tissues in specific anatomical locations. The existence of point specificity in acupuncture remains controversial (Choi 2012). Several clinical studies found that acupuncture at specific acupuncture points according to the traditional acupuncture theory have similar effects to the sham acupuncture points (including non-specific acupoints or non-acupuncture points) (Enblom 2012; Li 2012). Therefore, some researchers claimed that the location of the acupoints may not be as important as the stimulation techniques used as part of acupuncture treatment. However, there has also been some evidence to validate the acupoint specificity (Wang 2015; Yang 2014). Wang and colleagues demonstrated that the effectiveness of acupuncture for relieving visceral hypersensitivity was different at individual acupoints; the effects are more predominant at the acupoints on the stomach meridian (Wang 2015). Yang 2014 observed that the pattern of brain glucose metabolism change at the acupoint was pertinent and targeted, while at the non-acupoint it was disordered and randomised. Meanwhile, some studies had shown that specific acupoints have sensitisation in a particular disease state, which can reflect the disease and be used to treat it by stimulation with a specialised needle (He 2017; Yan 2017). The main cause of this argument is that the essence of meridians and acupoints remains unclear, so it is difficult to design a standard method as a non-active control. In the sham acupuncture used in relevant studies, it is difficult to avoid all the active ingredients of acupuncture methods. On the other hand, acupoint may be a three-dimensional structure, including the dermal, muscular, and neural components, as well as connective tissue and chemical aspects,

because the acupuncture signals induced by varying needling-depth stimulation may be transmitted through different neural pathways (Chen 2013; Wu 2015). Classical point locations that are frequently used are guided by the Chinese meridian theory, which states that there are 361 acupoints situated on the surface of the body. Tender points are also used by clinical acupuncturists.

A number of different acupuncture techniques have been developed including traditional manual acupuncture (MA), electroacupuncture (EA), acupuncture point injection, transcutaneous electrical acupoint stimulation (TEAS), and laser acupuncture (which involves low-intensity, non-thermal laser irradiation to stimulate acupuncture points). In clinical practice, the MA and EA techniques are widely used. MA involves inserting acupuncture needles into the skin, which are then twisted by hand until a feeling of 'deqi' (a sensation of soreness, heaviness, numbness, or distension) occurs in the area surrounding the needles. The EA technique involves delivering a stimulating current to the acupuncture points using an electrical stimulator. Typical acupuncture treatment involves the needles being left in place for up to 30 minutes, with multiple treatment sessions over several weeks.

There is a lack of consensus regarding the benefits of MA and EA, with some studies showing EA to have a superior analgesic effect (Lang 2010; Schliessbach 2011; Zheng 2010), and other studies showing no difference in pain reduction for MA and EA (Ahn 2011; Plaster 2014). Disagreement also exists regarding the effects of prolonged acupuncture stimulation, with research suggesting it can result in therapeutic benefit, but can also result in habituation and tolerance that weakens the beneficial effects of acupuncture (Han 2011; Leung 2008; Li 2014). One study demonstrated that the mean level of serum nitric oxide in people with migraine decreased by 31% after five acupuncture treatments (P value < 0.05) (Gündüztepe 2014). Other research has suggested that acupuncture is most effective when combined with another treatment, rather than as a stand-alone treatment (Lu 2011; Miao 2014).

How the intervention might work

The overwhelming data from basic science support the idea that acupuncture mediates its clinically relevant effects via nerves, usually, but not exclusively, in deep somatic tissue (Dhond 2008; Kim 2008; Zhang 2005). EA stimulates all fibre types, since all nerve impulses work through alterations in membrane potentials mediated via voltage-gated channels. MA mediates a mechanical stimulus, and therefore will only stimulate mechanosensitive nerve endings (Toda 2002; Zhao 2008). Release of adenosine via both techniques may mediate a local inhibition of nociceptive fibres (Goldman 2010). Some evidence suggests that in the central nervous system acupuncture may produce an analgesic effect by the deactivation of limbic areas (Hui 2010; Shi 2015). Alternatively, descending inhibitory modulation may also be regulated by acupuncture to enable the modulation of pain (Takeshige 1992).

Why it is important to do this review

Acupuncture has been increasingly used to treat chronic pain (including neuropathic pain) and is considered to be one of the most popular types of complementary alternative medicine available in Western healthcare (Barnes 2008), with a survey showing that 13% of adults in Europe and Israel have used acupuncture to treat chronic pain (Breivik 2006). However, uncertainty remains regarding the effectiveness and safety of acupuncture treatments despite a number of clinical trials being undertaken.

This review will use the methodological standards outlined in the *PaPaS Author and Referee Guidance for Pain Studies* (PaPaS 2012), which includes a definition of a reduction in pain intensity of 50% or more to identify improvements in co-morbid symptoms, quality of life, and function. This approach will assess the best available evidence to determine whether acupuncture provides beneficial treatment for neuropathic pain in adults.

OBJECTIVES

To assess the analgesic efficacy and adverse events of acupuncture treatments for chronic neuropathic pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included relevant randomised controlled trials (RCTs) with a treatment duration of eight weeks or longer. We only included studies published in a journal, with the exception of online summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We excluded studies that were non-randomised or quasi-randomised (e.g. allocation by odd or even date of birth), studies of experimental pain, case reports, and clinical observations.

Types of participants

Adults aged 18 years and above with one or more chronic neuropathic pain conditions including (but not limited to):

1. cancer-related neuropathy;
2. central neuropathic pain;
3. complex regional pain syndrome (CRPS) Type II;
4. HIV neuropathy;
5. painful diabetic neuropathy (PDN);
6. phantom limb pain;
7. postherpetic neuralgia (PHN);
8. postoperative or traumatic neuropathic pain;
9. spinal cord injury;
10. trigeminal neuralgia.

If we found studies of participants with more than one type of neuropathic pain, we planned to analyse results according to the primary condition. We excluded studies of migraine and headache as they are the subject of another Cochrane Review (Chronicle 2004). In studies where people had a mixture of other types of pain and neuropathic pain, we included a study only if the majority of participants (greater than 80%) had neuropathic pain.

Types of interventions

Acupuncture either given alone or in combination with other therapies, with acupuncture therapy defined as needle insertion and stimulation of somatic tissues for therapeutic purposes. When acupuncture is given in combination with other therapies, the therapy given to the acupuncture group has to also be given

to the control group. We included any stimulation based on needle insertion, for example, electrical stimulation (EA) and warm needling (involving the burning of mugwort on an acupuncture needle inserted in the skin or tissues below to heat the needle). We excluded other methods of stimulating acupuncture points without needle insertion (e.g. direct moxibustion, indirect moxibustion, heat-sensitive moxibustion, moxa burner moxibustion, crude drug moxibustion, or natural moxibustion). Therefore, we included moxibustion with needle insertion but excluded any other types of moxibustion alone.

We compared:

1. acupuncture versus sham acupuncture;
2. acupuncture versus treatment as usual;
3. acupuncture versus other active therapies (anything that is a planned comparison, e.g. exercise or drug therapy).
4. acupuncture combined with other active therapy versus other active therapy

We excluded studies that compared different forms of acupuncture. We also excluded studies with acupuncture assigned to each investigated group (e.g. acupuncture alone versus acupuncture plus adjuvant treatment).

Types of outcome measures

Primary outcomes

1. Participant-reported pain intensity at the end of treatment measured using a validated visual analogue scale (VAS) or categorical pain scale. We are particularly interested in the number of people who achieve 'no worse than mild pain' (Moore 2013a). We consider 3 out of 10 on a numerical rating scale, or 30/100 mm on a VAS, as 'no worse than mild pain' (Wiffen 2013).
2. Participant-reported pain relief at the end of treatment measured using a validated VAS or categorical pain scale. Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) defines at least 30% pain relief over baseline as moderate pain relief, and at least 50% pain relief over baseline as substantial pain relief in chronic pain (Dworkin 2008).

Secondary outcomes

1. Any pain-related outcome indicating some improvement
2. Withdrawals due to lack of efficacy, adverse events, and for any cause
3. Participants experiencing any adverse event
4. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics or consequences.
5. Specific adverse events, particularly somnolence and dizziness
6. Quality of life

'Summary of findings' table

We included 'Summary of findings' tables to present the main findings for all comparisons in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes:

- participant-reported pain intensity measured using a VAS (including the number of participants who achieved 'no worse than mild pain');
- pain relief (including the number of participants who achieved at least 50% pain relief from baseline);
- serious adverse events;
- quality of life (all scales reported).

We used the GRADE approach to assess the quality of evidence (Appendix 2; Schünemann 2011a, Schünemann 2011b; GRADEpro GDT 2015).

Search methods for identification of studies

Electronic searches

We searched the following databases on 14 February 2017, without language or date restrictions:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, issue 2) via the Cochrane Register of Studies Online (CRSO);
2. MEDLINE (via Ovid) 1946 to Feb week 1 2017;
3. Embase (via Ovid) 1974 to 2017 week 07;
4. Chinese databases: Chinese BioMedical Literature Database (CBM); China National Knowledge Infrastructure (CNKI); Chongqing Weipu (VIP); Wanfang Database.

The search strategies for CENTRAL, MEDLINE and Embase can be found in Appendix 3, Appendix 4 and Appendix 5. The search strategies for the Chinese databases are presented in Appendix 6, Appendix 7, Appendix 8, and Appendix 9.

Searching other resources

We reviewed the bibliographies of any RCTs and review articles that we identified. We also searched the following clinical trial databases in February 2017: The metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/mrct/), ClinicalTrials.gov (ClinicalTrials.gov), and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) to identify additional published or unpublished data. We did not contact investigators or study sponsors for unpublished studies.

Data collection and analysis

We performed separate analyses according to particular neuropathic pain conditions. We combined different neuropathic pain conditions in analyses for exploratory purposes only.

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We excluded studies that clearly did not satisfy the inclusion criteria, and we obtained full copies of the remaining studies. Two review authors (TYC and JZ) read the studies independently and reached agreement by discussion. We

did not anonymise the studies before assessment. We created a PRISMA flow chart (Moher 2009) and a 'Characteristics of included studies' table for each study, and noted the reasons for exclusion in the Characteristics of excluded studies tables.

Data extraction and management

Two review authors (ZYJ and YY) extracted data independently using a standard form and checked for agreement before entering the data into Review Manager 5 (RevMan 2014). Where a study was reported in more than one paper, we collated multiple reports of each study into a single data extraction form. We extracted data regarding the pain condition and number of participants treated, management of interventions, study design (placebo or active control), study duration and follow-up, analgesic outcome measures, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse event). We resolved any disagreement by discussion.

Assessment of risk of bias in included studies

Two review authors (HSC and SML) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and adapted from those used by Cochrane Pregnancy and Childbirth (Derry 2012a), with any disagreements resolved by discussion.

1. **Random sequence generation** (checking for possible selection bias). We assessed the method used to generate the allocation sequence as low risk of bias (any truly random process, e.g. random number table or computerised random number generation) or unclear risk of bias (the method used to generate sequence not clearly stated). We would not assess high risk of bias on this domain because non-randomised or quasi-randomised studies were excluded directly.
2. **Allocation concealment** (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance, during recruitment, or changed after assignment. We assessed the methods as low risk of bias (e.g. telephone or central randomisation or consecutively numbered, sealed, opaque envelopes), unclear risk of bias (method not clearly stated), or high risk of bias.
3. **Blinding of participants and outcome assessment** (checking for possible performance and detection bias). During the acupuncture application, the acupuncturist knows the group to which the participants belonged, therefore, we assessed the methods used to blind participants and outcome assessors. We assessed the methods as low risk of bias (study states that it was blinded and describes the method used to achieve blinding for participants, e.g. identical acupuncture needles matched in appearance (Takakura 2013)), unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved), or high risk of bias (no blinding or incomplete blinding).
4. **Incomplete outcome data** (checking for possible attrition bias due to the use of incomplete outcome data). We assessed the methods used to deal with incomplete data as low risk of bias (less than 10% of participants did not complete the study, or used appropriate modelling to impute missing data), unclear risk of bias (insufficient reporting of attrition), or high-risk of bias (drop out is greater than 10% and used 'completer-only' analysis).
5. **Selective reporting** (reporting bias due to selective outcome reporting). We assessed this as low risk of bias where the study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review had been reported in the pre-specified way, or if the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). We assessed this as high risk of bias when:
   a. not all of the study's pre-specified primary outcomes had been reported;
   b. one or more primary outcomes was reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not pre-specified;
   c. one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse event);
   d. one or more outcomes of interest in the review were reported incompletely, so that they could not be entered in a meta-analysis;
   e. and the study report did not include results for a key outcome that was expected to have been reported for such a study.
6. **Size of study** (checking for possible biases confounded by small size). We assessed studies as being at low-risk of bias (200 or more participants per treatment arm), unclear risk of bias (50 to 199 participants per treatment arm), or high-risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We calculated numbers needed to treat for additional beneficial outcomes as the reciprocal of the absolute risk reduction (ARR; McQuay 1998). For unwanted effects, the number needed to treat for an additional beneficial outcome (NNTB) became the number needed to treat for an additional harmful outcome (NNTH) and we calculated it in the same manner. For dichotomous outcomes, we calculated risk ratio (RR) with 95% CI; for continuous outcomes, we calculated mean difference (MD) with 95% CI.

Unit of analysis issues

For studies with multiple treatment arms and a single control arm, where the treatment arms were not combined for analysis, we split the number of control participants between comparisons.

The particular concern of cross-over studies is the carry-over effect. For the data extracted from a cross-over study, we only used data from the first period, unless the data from both arms had been reported in a manner suitable for alternative methods of analysis (Higgins 2011).

However, there were no studies that had more than two available arms or with cross-over design.

Dealing with missing data

We used intention-to-treat (ITT) analysis, and missing participants were assigned zero improvement wherever possible.

Assessment of heterogeneity

We dealt with methodological and clinical heterogeneity by combining studies with similar research design and examining similar conditions. We assessed statistical heterogeneity visually (L'Abbé 1987), and used the I^2 statistic (Higgins 2003). We interpreted an I^2 estimate greater than or equal to 75%, accompanied by a statistically significant Chi^2 statistic, as evidence of substantial levels of heterogeneity (Deeks 2011), in which case we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

As described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011), reporting biases occur when the reporting of research findings is influenced by the nature and direction of results. Funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects (Egger 1997). We would have employed funnel plots for outcomes if they had included 10 studies or more that reported relevant data.

Data synthesis

Due to the high possibility of heterogeneity for participants and interventions in this review, where possible we conducted meta-analysis using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses of different techniques of acupuncture practice (such as MA, EA, auricular acupuncture, and warm needling). We were unable to conduct this subgroup analysis, however, because all the included studies used MA. We also planned to conduct subgroup analysis of 'peripheral versus central pain' but we were unable to because there were insufficient data.

We will conduct these subgroup analysis in future updates if more data become available.

Sensitivity analysis

Where the data were sufficient, we conducted sensitivity analysis for primary outcomes to test the robustness of the results. As our measured outcomes were based on subjectively rated scales, we had planned to assess whether the quality of included studies influenced the pooled result by excluding studies with high risk of bias for blinding (performance and detection bias). We tested whether missing data influenced the results where the ITT analysis had been applied by assigning missing participants as zero improvement. We reported both sets of results and discussed them. However, we did not perform any sensitivity analysis due to insufficient data reported for primary outcomes in the included studies.

RESULTS

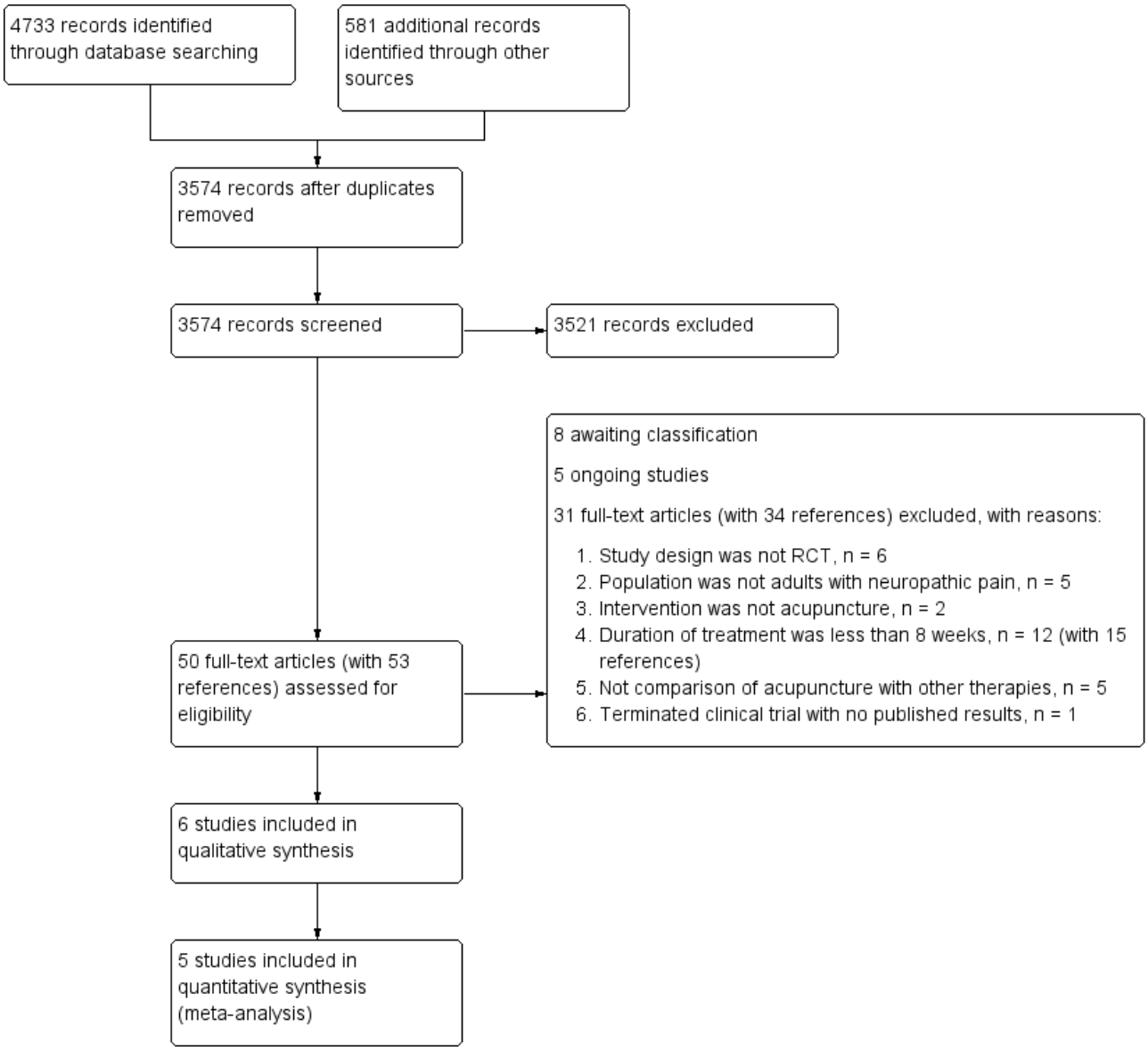
Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The initial search resulted in 5314 references in total, of which 4733 were identified from seven databases and 581 were identified through other sources. After checking for duplication, 3574 unique references remained. Upon inspection of the title and abstracts of these, we excluded a further 3521 references. We read the remaining 50 studies (with 53 references) in full, and we subsequently excluded 31 studies (with 34 references) with reasons (please refer to Figure 1 for further detail). Eight studies are awaiting assessment and five studies are ongoing. Eventually, we were able to include six studies in this review and five were included in the meta-analysis.

Figure 1. Study flow diagram



Included studies

Six RCTs with 462 participants (442 completers) met the inclusion criteria for this review. The sample sizes ranged from 59 to 104 (see Characteristics of included studies).

Participants

Most of the participants (n = 403) were recruited from China (Han 2017; Han 2017a; Wang 2016; Zhang 2010; Zhao 2016). The remaining 59 participants in Garrow 2014 were recruited from the UK.

The average age of included participants ranged from 52 to 63 years of age, and included 251 men and 191 women. Two studies (Garrow 2014; Han 2017) did not report the age and gender of the dropouts (n = 20). The included participants were diagnosed with peripheral neuropathic pain. The 358 participants in five studies (Garrow 2014; Han 2017a; Wang 2016; Zhang 2010; Zhao 2016) were diagnosed with diabetic peripheral neuropathy. The remaining 104 participants in Han 2017 were diagnosed with chemotherapy-induced peripheral neuropathy. Three studies (Garrow 2014; Han 2017; Han 2017a) did not report the length of illness of participants, while the remaining studies included participants with peripheral neuropathic pain for more than three months.

Interventions

One study (Wang 2016) had three treatment arms. We excluded one treatment arm in this study, as it did not meet our inclusion criteria. The remaining six studies had two treatment arms.

All six studies treated the intervention group with manual acupuncture (Garrow 2014; Han 2017; Han 2017a; Wang 2016; Zhang 2010; Zhao 2016). Manual acupuncture was used alone in four studies, compared with sham acupuncture (Garrow 2014) or Western medicine. Mecobalamin combined with nimodipine was used as a control in Han 2017a and Zhao 2016, and inositol was the control in Zhang 2010. Manual acupuncture combined

with mecobalamin was administered in Han 2017, compared with mecobalamin used alone. Manual acupuncture combined with Xiaoke bitong capsule was administered in Wang 2016, compared with Xiaoke bitong capsule used alone.

The details for acupuncture points used in included studies are outlined in Table 1. The treatment duration of all included studies ranged from 8 to 12 weeks.

Outcomes

Participant-reported pain intensity at the end of treatment

Two studies measured participant-reported pain intensity (Garrow 2014; Han 2017). Garrow 2014 measured pain intensity with a VAS from 0 to 100, so we transferred those data to 0 to 10 scale measurements. (See Table 2 for details of the scales used.)

Participant-reported pain relief at the end of treatment

No study reported this outcome.

Any pain-related outcome indicating some improvement

Three studies (Han 2017a; Wang 2016; Zhao 2016) reported any pain-related outcome, that was the number of participants who were judged to have 'no clinical response'. (See Characteristics of included studies for definition details.)

Withdrawal due to lack of efficacy, adverse effects or for any cause

Two studies reported withdrawals from the study (Garrow 2014; Han 2017) due to any cause.

Participants experiencing any adverse event

Only one study (Garrow 2014) reported participants experiencing any adverse event.

Participants experiencing any serious adverse event

No study reported this outcome.

Specific adverse events, particularly somnolence and dizziness

No study reported this outcome.

Quality of life

Two studies reported quality of life using different scales (Garrow 2014; Han 2017). (See Table 2 for details of scales used.)

Excluded studies

We excluded 31 studies (34 references) from this review for the following reasons (see Characteristics of excluded studies).

1. Issues relating to study design: we excluded six studies as they were not randomised controlled trials (Hu 2015; Schroeder 2012; Shen 2009; Tan 2004; Zhao 2009; Zheng 2014).
2. Issues relating to participants: we excluded five studies as the included participants were not adult patients with neuropathic pain (Chung 2016; Franca 2008; Koh 2013; MacPherson 2015; Tam 2007).
3. Issues relating to the intervention: two studies employed therapeutic methods that did not meet our criteria, like moxibustion or trigger-point injection (Ay 2010; Lin 2004). We also excluded 12 studies (15 references) because the treatment duration was less than eight weeks (Chen 2007; Dyson-Hudson 2007; Gao 2012; Itoh 2009; Itoh 2012; Liu 2013; Penza 2011; Sun 2014; Wang 2013; Zhang 2015; Zheng 2013; Zhu 2011).
4. Issues relating to comparison: we excluded five studies for this reason. Four studies reported acupuncture being given in combination with other therapies, but the same therapy was not given to the control group (Li 2010; Lin 2006; Zhang 2013; Zhou 2011). The fifth study was excluded as they compared different forms of acupuncture (Wang 2007).
5. In addition, we excluded one clinical trial (NCT01881932) as it was terminated with no published results.

Studies awaiting classification

See Characteristics of studies awaiting classification.

There were seven studies awaiting classification due to unclear treatment duration. The location of these studies were the USA (Maeda 2013), Germany (DRKS00010625) and China (chiCTR-INR-16009079; NCT02770963; NCT03048591; Shen 2016; Yue 2016). One study (Rivera 2010) based in Spain was not printed in English or Chinese and is awaiting translation.

Ongoing studies

See Characteristics of ongoing studies.

We identified five ongoing studies that started between 2007 and 2017 but had not been published. The location of these studies were the USA (NCT01163682; NCT02104466; NCT02831114), Korea (Shin 2011), and China (NCT02553863). Three studies (Shin 2011; NCT02104466; NCT02831114) were in the recruiting phase and the other two studies (NCT01163682; NCT02553863) had not yet started recruiting at the time of writing this review.

Risk of bias in included studies

Details of these assessments are available in the 'Risk of bias' table corresponding to each study in the Characteristics of included studies tables, and are also presented in the 'Risk of bias' graph (Figure 2) and summary (Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

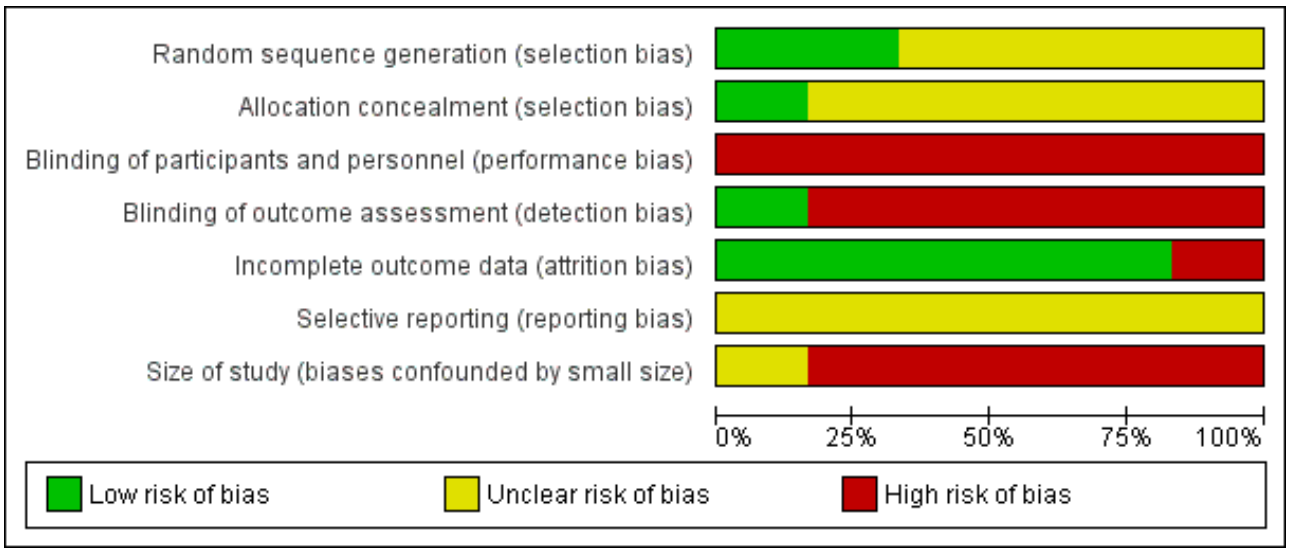
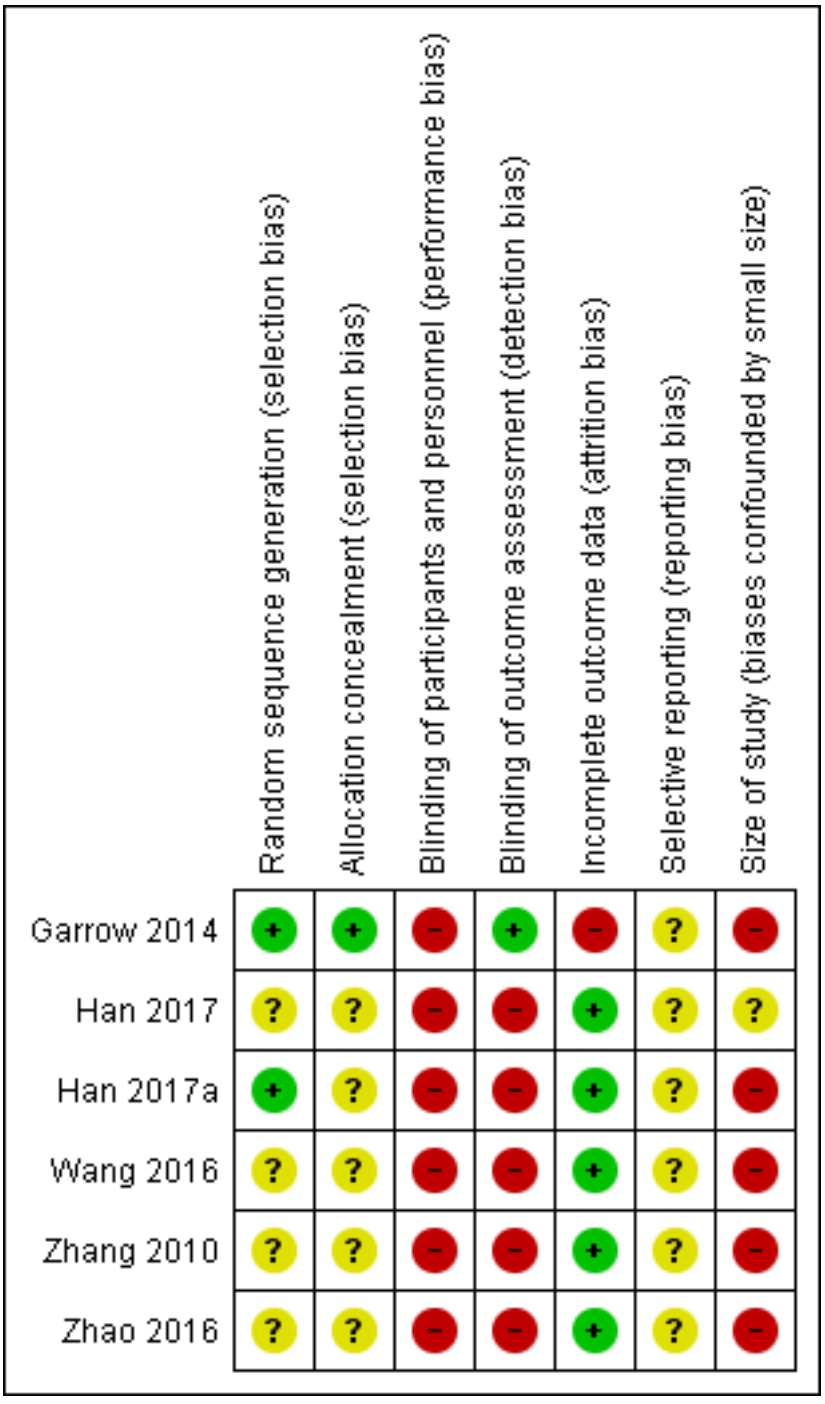


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study



Allocation

Random sequence generation

All six included studies reported some form of randomisation. Two studies reported adequate sequence generation and we rated them as low risk. The methods used to generate the allocation sequence included random number tables (Han 2017a), or computerised randomisation programs (Garrow 2014). The remaining four studies provided insufficient information to assess bias on this domain and we classified them as unclear risk of bias.

Allocation concealment

Only Garrow 2014 reported adequate allocation concealment. This study used sealed, opaque envelopes, managed by a person who was not involved with the study, to maintain allocation concealment. The remaining five studies did not provide enough information to rate this bias and so we classified them as unclear.

Blinding

We found all included studies had high risk of performance bias. For five studies (Han 2017; Han 2017a; Wang 2016; Zhang 2010;

Zhao 2016), participants in one group received acupuncture and the other group did not. It would not have been possible to blind participants and healthcare professionals giving the treatment. In the study Garrow 2014 (acupuncture versus sham acupuncture), the treatment allocation was revealed to the acupuncturists but out of sight of the participants.

We also rated all included studies, except for one (Garrow 2014, low risk), as high risk of detection bias in that the primary outcomes (e.g. pain intensity) were subjective measures and were reported by the participants themselves. The unblinding of the participants is likely to influence the detection of true effect. However, in the study Garrow 2014, it is possible that the participants had been blinded.

Incomplete outcome data

We rated five studies as low risk of bias in this domain: four studies did not have missing outcome data (Han 2017a; Wang 2016; Zhang 2010; Zhao 2016); and we rated the other one study as low risk (Han 2017) due to the fact that the proportion of dropout was less than 10% and reasons for dropout were not relevant to the effect of intervention. The dropout rate was higher than 10% in the study Garrow 2014 (14/59, 23.7%) and the study author only analyzed data from completers, and so we rated this study as high risk of attrition bias.

Selective reporting

The study protocols were not available and we rated all studies to be at unclear risk of reporting bias.

Size of study (biases confounded by small size)

We judged five studies to be at a high-risk of bias due to small sample size (fewer than 50 participants per treatment arm: Garrow 2014; Han 2017a; Wang 2016; Zhang 2010; Zhao 2016). We found the remaining study (Han 2017) to have an unclear risk of bias (52 participants per treatment arm).

Effects of interventions

See: **Summary of findings for the main comparison** Acupuncture versus sham acupuncture for neuropathic pain in adults; **Summary of findings 2** Acupuncture versus treatment as usual for neuropathic pain in adults; **Summary of findings 3** Acupuncture versus other active therapy for neuropathic pain in adults; **Summary of findings 4** Acupuncture combined with other active therapy versus other active therapy for neuropathic pain in adults

Comparison 1: acupuncture versus sham acupuncture

For this comparison, we found only one relevant study (Garrow 2014) involving 59 participants receiving either manual acupuncture or sham acupuncture. However, only 45 participants completed the assessment and were included in the analysis for pain intensity and quality of life.

See Summary of findings for the main comparison.

Primary outcomes

Participant-reported pain intensity

Garrow 2014 found no clear difference on VAS score of pain intensity between the manual acupuncture and the sham acupuncture groups (n = 45; MD -0.40, 95% CI -1.83 to 1.03; Table 3). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and attrition bias (high withdraw rates, and unbalanced as well), and high risk of bias confounded by small study size; and once for imprecision due to wide 95% CIs.

Participant-reported pain relief

The study did not explicitly report this outcome, but the average VAS score of the manual acupuncture and sham acupuncture groups was 5.8 and 6.2 respectively, indicating that neither group achieved 'no worse than mild pain'.

Secondary outcomes

Any pain-related outcome

The study did not report this outcome.

Withdrawals due to lack of efficacy, adverse events, and for any cause

The study reported that 14 participants withdrew from the study and were lost to follow-up. Three of these withdrew due to adverse events. Fewer dropouts (n = 4) were reported in the manual acupuncture group than the sham acupuncture group (n = 10), but no clear differences were observed (n = 59; RR 0.44, 95% CI 0.16 to 1.25; NNTB = 6; Table 4). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and attrition bias, and high risk of bias confounded by small study size; and once for imprecision due to wide 95% CI.

Participants experiencing any adverse event

The study did not find any notable differences between the manual acupuncture and sham acupuncture groups (n = 59; RR 0.55, 95% CI 0.05 to 5.78; NNTB = 34; Table 4). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and attrition bias, and high risk of bias confounded by small study size; and once for imprecision due to wide 95% CI.

Participants experiencing any serious adverse event

The study did not report this outcome.

Specific adverse events, particularly somnolence and dizziness

The study did not report this outcome.

Quality of life

The study found no clear differences on physical health score (n = 45; MD -0.20 95% CI -5.78 to 5.38), mental health score (n = 45; MD 3.50 95% CI -4.17 to 11.27) and bodily pain score (n = 45; MD 10.00 95% CI -3.13 to 23.13) (Table 3). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high-risk of performance and attrition bias, and high risk of bias confounded by small study size; and once for imprecision due to wide 95% CI.

We did not perform subgroup analysis or sensitivity analysis in this comparison due to insufficient data.

Comparison 2: acupuncture versus treatment as usual

We found no studies reporting data for this comparison.

Comparison 3: acupuncture versus other active therapy

For this comparison, we found three relevant studies (Han 2017a; Zhang 2010; Zhao 2016; n = 209) that compared manual acupuncture with other active therapy. The other active therapies were mecobalamin combined with nimodipine, and inositol.

Primary outcomes

Participant-reported pain intensity

No study reported this outcome.

Participant-reported pain relief

No study reported this outcome.

Secondary outcomes

Any pain-related outcome

The three relevant studies (Han 2017a; Zhang 2010; Zhao 2016) reported data for the number of participants with 'no clinical response'. There were fewer participants with no clinical response in the manual acupuncture group than in the 'Western medicine' group (n = 209; RR 0.25, 95% CI 0.12 to 0.51; NNTB = 4; Analysis 1.1). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and attrition bias, and high risk of bias confounded by small study size; and once for imprecision due to wide 95% CI.

Withdrawals due to lack of efficacy, adverse events, and for any cause

No study reported this outcome.

Participants experiencing any adverse event

No study reported this outcome.

Participants experiencing any serious adverse event

No study reported this outcome.

Specific adverse events, particularly somnolence and dizziness

No study reported this outcome.

Quality of life

No study reported this outcome.

We did not perform subgroup analysis or sensitivity analysis in this comparison due to insufficient data.

Comparison 4: acupuncture combined with other active therapy versus other active therapy

For this comparison, we found two relevant studies (Han 2017; Wang 2016; n = 164). The acupuncture technique that the studies employed was manual acupuncture. The other active therapies were mecobalamin, and Xiaoke bitong capsule.

See Summary of findings 4.

Primary outcomes

Participant-reported pain intensity

For this outcome, we found only one relevant study where pain was measured using VAS. Han 2017 reported that participants receiving manual acupuncture combined with mecobalamin had a lower VAS score of pain intensity than those receiving mecobalamin used alone (n = 104; MD -1.02, 95% CI -1.09 to -0.95; Table 3), but the average VAS score of the acupuncture and control groups were 3.23 and 4.25 respectively, indicating that neither group achieved 'no worse than mild pain'. We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and detection bias, and once for imprecision due to wide 95% CI.

Participant-reported pain relief

No study reported this outcome.

Secondary outcomes

Any pain-related outcome

For this outcome, we found only one relevant study (Wang 2016) that reported data for number of participants showing 'no clinical response'. We did not observe clear differences between the compared groups (n = 60; RR 0.40, 95% CI 0.14 to 1.14; NNTB = 5; Table 4). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and detection bias, and once for imprecision due to wide 95% CI.

Withdrawals due to lack of efficacy, adverse events, and for any cause

For this outcome, we found only one relevant study (Han 2017). There was no clear differences on withdrawals due to any cause when comparing acupuncture combined with other active therapy versus other active therapy used alone (n = 104; RR 1.00, 95% CI 0.21 to 4.73; Table 4). We judged the quality of evidence for this outcome to be very low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and detection bias, and once for imprecision due to wide 95% CI.

Participants experiencing any adverse event

No study reported this outcome.

Participants experiencing any serious adverse event

No study reported this outcome.

Specific adverse events, particularly somnolence and dizziness

No study reported this outcome.

Quality of life

One study (Han 2017) reported quality of life (the nervous system symptoms) assessed by Functional Assessment of Cancer Therapy/ Gynaecologic Oncology Group/ Neurotoxicity (FACT/the GOG-Ntx) questionnaire scores. Results showed that quality of life improved in the manual-acupuncture combined with mecobalamin group compared with the mecobalamin-alone group (n = 104; MD -2.19, 95% CI -2.39 to -1.99; Table 3). We judged the quality of evidence for this outcome to be low. We downgraded the quality of evidence twice for very serious limitations to study quality due to high risk of performance and detection bias.

We did not perform subgroup analysis or sensitivity analysis in this comparison due to insufficient data.

Assessment of reporting biases

None of the comparisons included 10 studies reporting the same outcome, so we did not produce a funnel plot to assess the reporting biases.

DISCUSSION

Summary of main results

When acupuncture was compared with sham acupuncture for neuropathic pain in adults, this review identified limited data with very low-quality evidence on pain intensity and quality of life, which showed no clear difference between groups (one study; Summary of findings for the main comparison). The average VAS score of the manual acupuncture and sham acupuncture groups was 5.8 and 6.2 respectively, indicating that neither group achieved 'no worse than mild pain'. Evidence was not available on pain relief, serious adverse events or other pre-defined secondary outcomes.

We did not find any study comparing acupuncture with treatment as usual.

When acupuncture alone was compared with other active therapy (mecobalamin combined with nimodipine, inositol), the manual acupuncture group had fewer participants with 'no clinical response' than those using mecobalamin combined with nimodipine, or inositol. Evidence was not available for primary outcomes or the remaining secondary outcomes.

When investigating acupuncture combined with other active therapy versus other active therapy used alone (mecobalamin, and Xiaoke bitong capsule), we found that participants who received the combination therapy had a lower VAS score on pain intensity and improved quality of life, than those who received other active therapy alone. However, the average VAS score of the acupuncture and control groups was 3.23 and 4.25 respectively, indicating that neither group achieved 'no worse than mild pain'. Furthermore, the evidence was obtained from a study with high risk of bias and a very small sample size (n = 104). There was no evidence about pain relief. We found no clear differences between groups on the remaining parameters, including 'no clinical response' withdrawals. However, we found no evidence about adverse events.

In general, no clear benefits or harms of acupuncture in neuropathic pain in adults were discernible due to the lack of robust evidence. Five studies are still ongoing and seven studies are awaiting classification due to unclear treatment duration, and the results of these studies may influence the current findings.

Overall completeness and applicability of evidence

Overall, the evidence is incomplete from several angles, including the participants, the interventions and the outcomes. All included participants were aged between 52 and 63 years (on average), and diagnosed with peripheral neuropathic pain; 77% of the participants were diagnosed with diabetic peripheral neuropathy, hence limiting the applicability of the findings. In terms of interventions, all included studies used manual acupuncture. Furthermore, other acupuncture techniques (such as EA, warm needling, fire needling) were not identified. Evidence for acupuncture compared with usual treatment was also lacking.

Most of the included studies did not report either or both of our two primary outcomes: no worse than mild pain and participant-reported pain relief.

Five of the six studies were conducted in China, where acupuncture is more frequently practiced and culturally recognised than in other countries, hence this may further limit the applicability of the findings.

Quality of the evidence

Overall, the quality of the evidence is very low, downgraded for study limitations (high risk of performance, detection and attrition bias, and high risk of bias confounded by small study size) or imprecision. All included studies except Garrow 2014 had high-risk of performance bias due to insufficient blinding of participants and personnel; as most of the outcomes were self-reported (assessed by participants), detection bias is also high. The only study rated as low risk of detection bias stated that the participants were blinded (Garrow 2014). Five included studies had small sample sizes (fewer than 50 participants per treatment arm), and one study had high risk of attrition bias. Most studies did not clearly describe the method of random sequence generation and allocation concealment. We identified potential reporting bias as we were unable to obtain the protocols for many of the included studies. The quality of the evidence for most outcomes was compromised by small sample size and imprecise summary effects. We have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

Potential biases in the review process

We developed comprehensive search strategies and performed the search using both Chinese and English databases. However, we only included published data so it is possible that there is publication bias. Two reviewers screened studies and extracted the data independently, and it is less likely that this process could have introduced bias.

Agreements and disagreements with other studies or reviews

A previous systematic review assessed the effectiveness of complementary therapies for neuropathic and neuralgic pain (Pittler 2008) and found that the evidence was not sufficient to address whether acupuncture can relieve neuropathic or neuralgic pain. Two additional systematic reviews explored acupuncture for trigeminal neuralgia (TN) (Liu 2010) and post-stroke shoulder pain (Lee 2016), respectively. Both reviews found that acupuncture had some effect for pain, however, the study duration was not limited in these reviews and the length of included studies in Lee 2016 was less than eight weeks. The authors found that all the eligible studies were of low quality and the results were inconclusive. The present review has very little evidence concerning acupuncture in neuropathic pain, and reached a similar conclusion to these previous reviews.

AUTHORS' CONCLUSIONS

Implications for practice

For people with neuropathic pain

No clear benefits or harms of acupuncture were observed in terms of pain intensity, pain relief and quality of life when compared to sham acupuncture or other therapies. These findings were based on small studies with very low-quality evidence and limited applicability. None of the interventions, whether acupuncture or control interventions, achieved 'no worse than mild pain'. Additionally, there is a lack of evidence on the safety parameters of acupuncture to enable a more comprehensive evaluation of benefit and harm.

For clinicians

Overall, there is insufficient evidence to support or refute the use of acupuncture in the treatment of neuropathic pain in general, or for any specific neuropathic pain condition.

For policy makers and funders

The effectiveness of acupuncture compared to sham acupuncture or other therapies remains unclear due to the sparse data. This review revealed a lack of good-quality evidence that hinders effective decision making. For example, evidence was missing on younger adults, people with diverse types of neuropathic pain, the use of different acupuncture techniques, and most importantly, the availability of clinically relevant outcomes.

Implications for research

General implications

Linde 2010 estimates that to adequately power a clinical trial with two parallel arms of acupuncture versus sham in chronic pain, it would require 800 participants in total. In neuropathic pain it is likely an even greater number of participants would be needed. However, if this sample size is not practical, studies with larger sample size (for instance 200) are required. We also suggest more pragmatic trials that test acupuncture against or in addition to other active therapies as a first step in people with general neuropathic pain (not just peripheral neuropathic pain). Future studies could assess acupuncture techniques other than manual acupuncture, such as warm needle acupuncture or electroacupuncture, compared with sham acupuncture or other active therapies.

Design

Future RCTs should be designed with more than eight weeks of treatment duration to explore any changes in neuropathic pain outcomes. Blinding is encouraged to minimise the risk of performance and detection biases.

Other

The generation of the allocation sequence and allocation concealment is a fundamental part of study methodology and should be reported. Studies should follow the CONSORT statement (Schulz 2010) or Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) (MacPherson 2001) when reporting clinical trials.

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Parts of this review were generated using Review Manager HAL 4.3 Beta. You can find more information about RevMan HAL here (RevMan HAL 2015).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Garrow 2014

Methods	Allocation: randomisation Blinding: single-blind Study duration: 10 weeks Location: Greater Manchester, UK
Participants	Diagnosis: PDN Total: n = 59 Sex: 31 male, 14 female Age (years old): mean = 68, SD = 11.1 in acupuncture group; mean = 63, SD = 10.8 in control group Length of illness: not stated **Inclusion criteria**: people with type 1 or type 2 diabetes, aged 18-80 years, with a clinical diagnosis of PDN and taking a prescribed drug for PDN were identified from primary and secondary care patient databases and invited to attend a screening visit held in the recruiting centre of a local district general hospital. Other inclusion criteria were patients taking a prescribed drug for their neuropathic pain; having at least one palpable pedal pulse per foot; not having previously received acupuncture treatment for PDN; being free of foot ulcers at the start of the study and having signs of peripheral sensory neuropathy, defined as the absence of any two of sharp/blunt sensations (measured using a NeuroTip); im-

Garrow 2014 *(Continued)*

	paired light touch (10 g monofilament) or a vibration-perception threshold on either foot > 25 V, measured with a neurosthesiometer. **Exclusion criteria**: not stated
Interventions	**1. Acupuncture group**: (n = 28) Management: A total of 5 standardised acupuncture points on the foot and lower limb of each leg (total 10) were used in the study. The chosen points were based on traditional Chinese medicine. The point location and depth of needle insertion were based on traditional acupuncture methods and good clinical practice. The depth of needle insertion varied according to point, but was usually 0.5-1.5 cun (about 0.25-2 cm). After insertion, the needles remained in place for 30 min and real needles were manipulated after 15 min Delivered by: acupuncturist Treatment duration: 10 weeks **2. Sham acupuncture group**: (n = 31) Management: sham needle was blunt and slid into the handle rather than penetrating the skin when the needle was tapped. Before needling, a sliding plastic tube was adhered to each of the acupuncture points to mask the allocation of needles from the participants. Participants not asked whether they felt deqi to avoid the risk of participants in the placebo group becoming unblinded to their treatment allocation. After insertion, the needles remained in place for 30 min and sham needles were manipulated after 15 min, which is in keeping with normal acupuncture practice. Delivered by: acupuncturist Treatment duration: 10 weeks
Outcomes	Pain intensity: VAS Withdrawals from trial due to any reason Any adverse events Quality of life: SF-36 (physical component score, mental component score, bodily pain score) --Unable to use The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale (measuring the likelihood of pain induced by neuromechanism), Sleep Problem Scale, MYMOP scores, Resting systolic BP, Resting diastolic BP.
Notes	Study funding sources: The National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (grant reference number PBPG-0706-10595). "The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before the recruitment, a computer-generated randomised list of numbers was prepared allocating participants to receive either real or sham acupuncture." (p.243) Comments: the investigators describe a random component in the sequence generation process.
Allocation concealment (selection bias)	Low risk	Quote: "The allocation was placed inside sequentially ordered sealed opaque envelopes, opened only after enrolment" (p.243)

Garrow 2014 *(Continued)*

		Comments: participants and investigators enrolling participants could not foresee assignment because of sealed, opaque envelopes used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The treatment allocation was revealed to the acupuncturists out of sight of the participants to ensure blinding. To reduce the risk of observer bias, the acupuncture practitioners were discouraged from discussing the treatments or previous results with the patients." (p.243) Comments: trialists were not blinded to the treatment allocation but participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatment allocation was revealed to the acupuncturists out of sight of the participants to ensure blinding. To reduce the risk of observer bias, the acupuncture practitioners were discouraged from discussing the treatments or previous results with the patients." (p.243) Comments: the above statement indicates that observers (or assessors) were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comments: A total of 4 participants (4/28, 14.3%) in the active group and 10 participants (10/31, 32.3%) in the sham group failed to complete the study. Missing outcome data was not balanced in numbers across intervention groups.
Selective reporting (reporting bias)	Unclear risk	Comments: the protocol of this study was not available. Insufficient information to permit judgement of low risk or high risk
Size of study (biases confounded by small size)	High risk	Comments: fewer than 50 participants per treatment arm

Han 2017

Methods	Allocation: randomisation Blinding: not stated Study duration: 84 days Location: Hangzhou, Zhejiang, China
Participants	Diagnosis: chemotherapy-induced PN Total: n = 104 (6 dropouts) Sex: male 56, female 42 Age (years old): mean = 63.9 Length of illness: not stated **Inclusion criteria**: diagnosed multiple myeloma (MM); baseline without PN and PN appeared after chemotherapy at ≥ grade II (according to the NCI CTCAE version 3.0 neuropathy severity assessment); EMG examinations showing disturbances in median and peroneal nerve conduction; platelet count > 30×10^9/L; no history of mecobalamin allergy; having discontinued chemotherapy within 3 months and were willing to accept new therapy and sign an informed consent form **Exclusion criteria**: pregnancy; severe heart, liver or kidney dysfunction or other severe diseases (e.g. malignancies); neuropathy caused by tumor compression, nutritional disorders or infections or causes other than chemotherapy; refusal to sign the informed consent form

Han 2017 *(Continued)*

Interventions	**1. Acupuncture + mecobalamin group**: (n = 52) Management: participants received only 500 µg mecobalamin intramuscularly every other day, 10 times and thereafter 500 µg orally 3/day. In addition, every participant received needles bilaterally in acupoints. The first acupuncture was in prone position acupoints with needle retention, followed by supine position acupoints. An aseptic procedure was executed with disposable, stainless steel 30-32 gauge needles, which were implanted to a depth of 0.3-1.0 inches (about 0.76-2.54 cm) into the acupoints until the participant felt dull pain or deqi, and were left in place for 30 min. The acupunctures were done daily for 3 days, then once every alternate day for 10 days as a treatment cycle. Each cycle was repeated every 28 days and the complete treatment included 3 cycles. Treatment duration: 84 days **2. Mecobalamin group**: (n = 52) Management: participants received the same mecobalamin application as above.
Outcomes	Pain intensity: VAS Withdraw from trial due to any cause Quality of life (FACT/the GOG-Ntx questionnaire scores) --Unable to use (not in protocol) Nerve conduction velocity
Notes	Study funding sources: the study was financially supported by grants from the Administration of Traditional Chinese Medicine Science and Technology Program of Zhejiang Province, Program Number: 2010ZA057, 2014ZB060; the Science and Technology Project of the Health Department of Zhejiang Province, Program Number: 2013KYA071; and the National Natural Science Foundation of China, Program Number: 81471532, 81402353.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...were randomly divided into two groups." (p.3) Comments: the investigators describe a random component in the sequence generation process, but no details stated on random methods
Allocation concealment (selection bias)	Unclear risk	Comments: the author did not describe the allocation concealment. Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comments: although the author did not describe the blinding of participants and personnel, it would not have been possible to blind participants and personnel who were giving the intervention because one group did not receive acupuncture.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of outcome assessment, the outcomes which were participant-reported would have detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: a total of 3 participants (3/52, 5.8%) in the treatment group and 3 participants (3/52, 5.8%) in the control group left the trial or were lost to follow-up, but reasons for dropout were not related to the intervention
Selective reporting (reporting bias)	Unclear risk	Comments: the protocol of this study was not available. Insufficient information to permit judgement of low risk or high risk

Han 2017 *(Continued)*

Size of study (biases confounded by small size)	Unclear risk	Comments: 50-199 participants per treatment arm

Han 2017a

Methods	Allocation: randomisation Blinding: not stated Study duration: 8 weeks Location: Lankao, Henan, China
Participants	Diagnosis: DPN Total: n = 84 Sex: male 57, female 27 Age (years old): mean = 56.3 Length of illness: not stated **Inclusion criteria**: people with diabetes, accompanied by remote sense obstacle, weaker muscles, tendon slow and dyskinesia. **Exclusion criteria**: PN caused by liver and kidney diseases
Interventions	**1. Manual acupuncture group**: (n = 42) Management: participants received acupuncture once daily for 8 weeks (2 courses). Participants were maintained at supine position. Number 28 needle inserted acupoint for 0.5-1 cun, retaining the needle for 30 min, hand-manipulating needle twice Treatment duration: 8 weeks **2. Western medicine group**: (n = 42) Management: participants received mecobalamin (500 ug, once daily) and nimodipine (40 mg, 3 times daily) for 8 weeks (2 courses)
Outcomes	Any pain-related outcome: no clinical response* --Unable to use (not in protocol) Motor nerve conduction velocity (MNCV); Sensory nerve conduction velocity (SCV)
Notes	*No clinical response: no improvement or worse on pain and numbness of body, disturbance of perception (touch and thalposis), delay of response to stimulus and no increase in nerve-conduction velocity Study funding sources: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...assigned randomly into control and observation groups according to random number table..." (p.47) Comments: the investigators described a random component in the sequence generation process.

Han 2017a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comments: the study author did not describe the allocation concealment. Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comments: although the author did not describe the blinding of participants and personnel, it would not have been possible to blind participants and personnel giving the intervention because one group did not receive acupuncture.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of outcome assessment, most of the outcomes were participant self-reported, hence would have detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comments: the protocol of this study was not available. Insufficient information to permit judgement of low risk or high risk
Size of study (biases confounded by small size)	High risk	Comments: fewer than 50 participants per treatment arm

Wang 2016

Methods	Allocation: randomisation Blinding: not stated Study duration: 12 weeks Location: Changchun, Jilin, China
Participants	Diagnosis: DPN Total: n = 90 Sex: male 44, female 46 Age (years old): mean = 56.4, SD = 5.45 in acupuncture group; mean = 55.4, SD = 7.28 in Xiaoke bitong capsule group; mean = 55.8, SD = 6.46 in lipoic acid capsule group Length of illness: 3 months-11 years **Inclusion criteria**: participants corresponding to diagnosis standards, strict diet control, stable amount of exercise over 2 weeks and receiving conventional glucose- lowering treatment (fasting blood glucose ≤ 7.0 mmol/L, 2-hour post-meal blood glucose ≤ 10.0 mmol/L, glycosylated haemoglobin < 7%, normotension and ortholiposis) **Exclusion criteria**: patients received relevant drugs for treatment of DPN within 2 weeks before enrolment; haemorrhage tendency within 2 months before enrolment; diabetic ketosis, ketoacidosis or infection within 1 month before enrolment; PN caused by other reasons; severe underlying diseases (e.g. liver and kidney dysfunction, cardiac insufficiency, myocardial infarction, cerebrovascular disease, malignant tumour); hyperglycemia caused by hyperthyroidism or hepatitis; women during gestation or lactation; systolic pressure ≥ 160 mmHg and/or diastolic pressure ≥ 100 mmHg; mentally disturbed or poor compliance; drug allergy history or allergic constitution
Interventions	**1. Acupuncture + Xiaoke bitong capsule group**: (n = 30) Management: participants received Xiaoke bitong capsule (1.2 g per time, 3 times daily) orally before 3 meals for 12 weeks. In addition, participants received acupuncture (retaining the needle for 30 min,

Wang 2016 *(Continued)*

	hand-manipulating of needle once before end) once daily (one course for 4 weeks, course interval was 3-5 days) Treatment duration: 12 weeks **2. Xiaoke bitong capsule group**: (n = 30) Management: participants received Xiaoke bitong capsule same as above **3. Lipoic acid capsule group**: (n = 30)* Management: participants received lipoic acid capsule (0.2 g per time, 3 times daily) orally before 3 meals for 12 weeks
Outcomes	Any pain-related outcome: no clinical response** --Unable to use (not in protocol) Biochemical criterion; nerve conduction velocity; markers of oxidative stress
Notes	*we did not use the data from this group, as it did not meet our inclusion criteria. **no clinical response: no improvement on the TCM symptoms (reduced score of syndrome < 30%) Study funding sources: key project of Administration of Traditional Chinese Medicine of Jilin Province (No: 2014- ZD2); Project of Health and Family Planning Commission of Jilin Province (No: 2015ZFZC06)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly divided into..." (p.51) Comments: the investigators described a random component in the sequence generation process, but no details stated on random methods
Allocation concealment (selection bias)	Unclear risk	Comments: the study author did not describe the allocation concealment. Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of participants and personnel, it would not have been possible to blind participants and personnel who delivered the intervention because one group did not receive acupuncture
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of outcome assessment, those outcomes that were participant self-reported would have detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comments: the protocol of this study was not available. Insufficient information to permit judgement of low risk or high risk
Size of study (biases confounded by small size)	High risk	Comments: fewer than 50 participants per treatment arm

Zhang 2010

Methods	Allocation: randomisation Blinding: not stated Study duration: 3 months Location: Liaoning, China
Participants	Diagnosis: DPN Total: n = 65 Sex: male 28, female 37 Age (years old): mean = 52.5 Length of illness: 0.5-5 years **Inclusion criteria**: participants conformed to the diagnostic criteria stipulated by WHO in 1999: FBG (fast blood glucose) ≥ 7.0 mmol/L, in the OGTT test 2 h BG ≥ 11.1 mmol/L or the random BG ≥ 11.1 mmol/L (all taking venous blood). The symptoms and signs were sustained pain and/or abnormal sensation in the four limbs (at least in the lower limbs), weakened reflex in 1 or both ankles, weakened sensation of vibration (sensation of vibration in inner ankle was weaker than that in entocnemial condyle), and decreased nervous conductive velocity (NCV) on the main side in electroneuro-physiological examination. Exclusion criteria: PN caused by other factors (such as heredity, alcoholism, uraemia, infection, malnutrition, drug intoxication and metal intoxication)
Interventions	**1. Conventional treatment of diabetes + acupuncture group**: (n = 32) Management: participants were conventionally treated with FBG < 7.0 mmol/L and 2 h BG below 11.1 mmol/L. For those with diabetes complicated with hypertension and hyperlipaemia, their BP and blood lipid were controlled to the normal range. Diet was rationally controlled. Number 30 1-1.5 cun filiform needles were used for acupuncture with the uniform reinforcing-reducing method. After the needles had been inserted into the points, evenly lifting, thrusting and twirling was performed until the participants felt needling sensation. Then, the needles were retained for 25 min, and manipulated twice. Treatment duration: once/day, with 14 sessions as 1 course of treatment, for 5 consecutive courses with a 4-day interval between courses **2. Conventional treatment of diabetes + inositol group**: (n = 33) Management: the same conventional treatment as above. Participants received oral-taken Inositol. Treatment duration: 2 g/day in 3 times for 3 months.
Outcomes	Any pain-related outcome: no clinical response*
Notes	*no clinical response: subjective symptoms were not improved or even aggravated Study funding sources: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups" (p.13) Comments: the investigators described a random component in the sequence generation process, but no details stated on random methods

Zhang 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comments: the study author did not describe the allocation concealment. Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of participants and personnel, it would not have been possible to blind participants and personnel who delivered the intervention because one group did not receive acupuncture
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of outcome assessment, those outcomes that were participant-reported would have detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comments: the protocol of this study was not available. Insufficient information to permit judgement of low risk or high risk
Size of study (biases confounded by small size)	High risk	Comments: fewer than 50 participants per treatment arm

Zhao 2016

Methods	Allocation: randomisation Blinding: not stated Study duration: 8 weeks Location: Weinan, Shaanxi, China
Participants	Diagnosis: Type 2 diabetes, DPN Total: n = 60 Sex: male 35, female 25 Age (years old): mean = 53, SD = 9.2 Length of illness: 3 months to 27 months **Inclusion criteria**: not stated **Exclusion criteria**: not stated
Interventions	**1. Acupuncture group**: (n = 30) Management: participants received acupuncture once daily for 8 weeks (2 courses). Participants were maintained at supine position. Number 28 needle inserted acupoint for 0.5-1 cun, retaining the needle for 30 min, hand-manipulating of needle twice Treatment duration: 8 weeks **2. Western medicine group**: (n = 30) Management: participants received mecobalamin (500 μg, once daily) and nimodipine (30 mg, 3 times daily) for 8 weeks (2 courses)
Outcomes	Any pain-related outcome: no clinical response*

Zhao 2016 *(Continued)*

	--Unable to use (not in protocol) motor nerve conduction velocity; Sensory nerve conduction velocity
Notes	*no clinical response: no improvement or worse on pain and numbness of body, disturbance of perception (touch and thalposis), delay of response to stimulus and no increased in nerve-conduction velocity Study funding sources: special research project of Department of Education of Shaanxi Province (14JK1256)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly divided into..." (p.97) Comments: the investigators describe a random component in the sequence generation process, but no details stated on random methods
Allocation concealment (selection bias)	Unclear risk	Comments: the study author did not describe the allocation concealment. Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of participants and personnel, it would not have been possible to blind participants and personnel who delivered the intervention because one group did not receive acupuncture
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comments: although the study author did not describe the blinding of outcome assessment, those outcomes that were participant-reported would have detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comments: the protocol of this study was not available. Insufficient information to permit judgement of low risk or high risk
Size of study (biases confounded by small size)	High risk	Comments: fewer than 50 participants per treatment arm

BP: blood pressure; **cun**: measure of patient's thumb width at the knuckle to derive acupoint; **DPN**; diabetic peripheral neuropathy; **EMG**: electromyography; **MYMOP**: Measure Yourself Medical Outcome Profile; **n**: number; **PDN**: painful diabetic neuropathy; **PN**: peripheral neuropathy; **SD**: standard deviation; **TCM**: traditional Chinese medicine; **VAS**: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ay 2010	The intervention was local anaesthetic injection
Chen 2007	Treatment duration < 8 weeks
Chung 2016	Participants had carpal tunnel syndrome symptoms, no indication of neuropathic pain in full text
Dyson-Hudson 2007	Treatment duration < 8 weeks

Study	Reason for exclusion
Franca 2008	Participants had tension neck syndrome, no indication of neuropathic pain in full text
Gao 2012	Treatment duration < 8 weeks
Hu 2015	Quasi-randomised study, randomisation based on the admission sequence
Itoh 2009	Treatment duration < 8 weeks
Itoh 2012	Treatment duration < 8 weeks
Koh 2013	Participants had adhesive capsulitis, no indication of neuropathic pain in full text
Li 2010	Compared TCM + acupuncture with carbamazepine
Lin 2004	The intervention was needle scalpel, not acupuncture
Lin 2006	Compared acupuncture + acupuncture point injection with amitriptyline
Liu 2013	Treatment duration < 8 weeks
MacPherson 2015	Participants had chronic neck pain, no indication of neuropathic pain in full text
NCT01881932	Terminated study with no publication
Penza 2011	Treatment duration < 8 weeks
Schroeder 2012	Non-randomised, non-blinded study
Shen 2009	Quasi-randomised study, randomisation based on the admission sequence
Sun 2014	Treatment duration < 8 weeks
Tam 2007	Participants had rheumatoid arthritis, no indication of neuropathic pain in full text
Tan 2004	Quasi-randomised study, randomisation based on the admission sequence
Wang 2007	Compared different acupuncture (miniscalpel-needle vs trigger-point injection)
Wang 2013	Treatment duration < 8 weeks
Zhang 2013	Compared combined therapy mainly based on acupuncture (electroacupuncture + acupoint injection + He-Ne laser therapy) with Western medicine
Zhang 2015	Treatment duration < 8 weeks
Zhao 2009	Quasi-randomised study, randomisation based on the admission sequence
Zheng 2013	Treatment duration < 8 weeks
Zheng 2014	Quasi-randomised study, randomisation based on the admission sequence
Zhou 2011	Compared acupuncture + manipulation with nerve block
Zhu 2011	Treatment duration < 8 weeks

TCM: traditional Chinese medicine

Characteristics of studies awaiting assessment *[ordered by study ID]*

chiCTR-INR-16009079

Methods	Allocation: randomised, parallel, controlled trial Blinding: blind method was implemented for statistical personnel Study duration: not stated Location: Zhejiang, China
Participants	Diagnosis: Multiple myeloma with PN Total: n = 104 Sex: male and female Age: range: 32-81 years old Length of illness: not stated **Inclusion criteria**: diagnosed MM; baseline without peripheral neuropathy and peripheral neuropathy appeared after chemotherapy (including thalidomide and bortezomib therapy) with ≥ level 2 (according to the NCI CTCAE version 3.0 neuropathy severity assessment) and EMG examinations showing disturbances of the median and peroneal nerve conductions; platelet count > 30 × 10^9/L and no history of mecobalamin allergy; discontinued bortezomib and thalidomide within 3 months; met the above criteria and willing to accept this therapy and signed the informed consent **Exclusion criteria**: pregnancy; severe heart, liver, kidney dysfunctions, or other severe diseases (e.g. malignancies); 3neuropathy caused by tumor compression, nutritional disorders or infections and other than the chemotherapy; refused to sign the informed consent
Interventions	**1. Acupuncture combined with mecobalamin group**: (n = 52) **2. Mecobalamin alone group**: (n = 52).
Outcomes	Pain intensity: neuralgia score Quality of life: daily activities score --Unable to use Conduction velocities (not in protocol)
Notes	Awaiting classification due to unclear treatment duration

DRKS00010625

Methods	Allocation: RCT Blinding: open-label Study duration: 28 weeks Location: Germany
Participants	Diagnosis: drug-induced polyneuropathy Total: not stated Sex: male and female

DRKS00010625 *(Continued)*

	Age: > 18 years Length of illness: not stated **Inclusion criteria**: clinically diagnosed chemotherapy-induced PN, pathologic results of the sural nerve in NCS. **Exclusion criteria**: current chemotherapy treatment or restart of chemotherapy due to tumor recurrence; other diseases that may cause PN; history of epilepsy; coagulopathy or use of anticoagulants with bleeding time > 3 min, prothrombin time < 40%, platelet count < 50.000/µL or partial thromboplastin time > 50 s; bacterial infection or other skin diseases at the lower extremities; bone fracture of the lower extremities during the last 3 months; alcohol, opiate, analgesic, or drug abuse; psychiatric illnesses other than mild depression; incapable of following the study instructions; (severe language disturbances, serious cognitive deficits, lack of time); pregnant or breast-feeding women; current participation in other clinical studies
Interventions	**1. Acupuncture group**: Management: 10 acupuncture treatments during the first study period. NCS are performed before and after the treatment period. In the second study period, participants do not receive specific treatment but NCS at the end of the period. **2. Wait-list group**: Management: wait-list without specific treatment during the first study period. NCS are performed before and after the period. During the second study period, participants receive 10 acupuncture treatments. NCS are repeated after the treatment period
Outcomes	Pain intensity: Total Neuropathy Score; Symptom-related numerical rating scale questionnaire --Unable to use (not in protocol) Sensory sural nerve action potential amplitude (SNAP) as measured by NCS; motor tibial nerve action potential amplitude; sural and tibial nerve conduction velocity as measured by NCS
Notes	Awaiting classification due to unclear treatment duration

Maeda 2013

Methods	Allocation: randomised Blinding: not stated Study duration: bot stated Location: USA
Participants	Diagnosis: Carpal tunnel syndrome Total: n = 59 Sex: male 10; female 49 Age: mean ˜ 49.1 years; SD ˜ 9.8 years Length of illness: > 3 months **Inclusion criteria**: all participants were examined for eligibility by a psychiatrist at Spaulding Rehabilitation Hospital, which included a physical exam for Phalen's maneuver and Durkan's sign and testing of median and ulnar sensory nerve conduction (NCS: Cadwell Sierra EMG/NCS Device, Kennewick, WA). NCS inclusion criteria consisted of median nerve sensory latency > 3.7 milliseconds or median nerve sensory latency > 0.5 milliseconds compared to ulnar nerve.

Maeda 2013 *(Continued)*

	Exclusion criteria: contraindications to MRI, history of diabetes mellitus, cardiovascular, respiratory, or neurological illnesses, rheumatoid arthritis, wrist fracture with direct trauma to median nerve, current usage of prescriptive opioid medication, thenar atrophy, previous acupuncture treatment (manual, EA, and TENS) for carpal tunnel syndrome, nerve entrapment other than median nerve, cervical radiculopathy or myelopathy, generalised PN, blood dyscrasia or coagulopathy or current use of anticoagulation therapy. History of axis I psychiatric diagnosis (substance use disorder, psychotic disorder, or bipolar disorder), and use of psychotropic medications were also exclusions for this study.
Interventions	**1. Local verum electroacupuncture group**: (n = 22) **2. Distal verum electroacupuncture group**: (n = 18) **3. Sham electroacupuncture group**: (n = 19)
Outcomes	Pain intensity: VAS; the intensity of acupuncture-evoked sensations after the scan session using the MGH Acupuncture Sensation Scale (MASS) instrument --Unable to use (not in protocol) Functional imaging (functional MRI) data
Notes	Awaiting classification due to unclear treatment duration

NCT02770963

Methods	Allocation: randomised Blinding: double blind (participant, outcomes assessor) Study duration: 28 weeks Location: Beijing, China
Participants	Diagnosis: discogenic sciatica Total: estimated enrolment = 60 Sex: male and female Age: Range: 18-75 years Length of illness: not stated **Inclusion criteria**: unilateral leg pain diagnosed as discogenic sciatica; sciatica patients with an average leg pain VAS of ≥ 40 mm in the last 24 h; aged 18-75 years; leg pains that correlated with CT or MRI findings of lumbar disc herniation; agreed to follow the trial protocol. **Exclusion criteria**: severe cases with central or giant or ruptured lumbar disc herniation, cauda equina syndrome, foot drop, or surgery requirements; progressive neurological symptoms after 3 months of strict conservative treatment (e.g. nerve root adhesion, crossed straight-leg testing, or obvious muscle atrophy); severe cardiovascular, liver, kidney, hematopoietic system diseases, autoimmune diseases, or poor nutritional status; cognitive impairment; pregnancy; subjects who received acupuncture for sciatica within the past month
Interventions	**1. Acupuncture group**: (n = 30) **2. Sham Acupuncture group**: (n = 30)
Outcomes	Pain intensity: change in mean weekly VAS of leg pain and low back pain; Oswestry disability index;

NCT02770963 *(Continued)*

	Serious adverse events Quality of life: patients' global impressions of improvement; --Unable to use (not in protocol) Participants' expectations for acupuncture; blinded evaluation as measured by participant questioning of whether they believed they received real acupuncture at week 4
Notes	Awaiting classification due to unclear treatment duration

NCT03048591

Methods	Allocation: randomised Blinding: blind to outcomes assessor Study duration: 3 months Location: Tianjin, China
Participants	Diagnosis: chemotherapy-induced PN Total: estimated enrolment = 36 Sex: male and female Age: Range: 18-80 years old Length of illness: not stated **Inclusion criteria**: histopathological and/or cellular pathology results prove malignancy of the tumour and the participant has received chemotherapy treatment before; 15 weeks after the completion of chemotherapy, the limbs are still feeling abnormal and the symptoms fulfil WHO grade 2 or more; Zubrod - Eastern Cooperative Oncology Group-WHO (ZPS) grade 0-2, cardiac function, liver function and renal function are not significantly abnormal, the survival period of the participant is expected to be > 6 months; gender unrestricted, aged 18-80 years; voluntary participation in the study, willing to sign informed consent, willing to comply with randomised grouping, willing to follow-up. **Exclusion criteria**: suffering from PN due to infection, radiotherapy, HIV, chronic alcoholism, hypothyroidism, diabetes, paraneoplastic syndrome or other diseases or are suffering from nervous system diseases; being treated with other drugs that may lead to neurotoxicity; blood coagulation disorder; pregnancy and lactating women; infection, scarring or defects near the acupoint sites; received intervention for the prevention and treatment of peripheral neuropathy 2 weeks before screening or has received TCM (acupuncture, moxibustion, cupping, Chinese medicine therapy 1 month before
Interventions	**1. Electroacupuncture group** **2. No intervention**
Outcomes	Quality of life: questionnaire to assess chemotherapy-induced PN (QLQ-CIPN20); Functional Assessment of Cancer Treatment - General scale (FACT-G)
Notes	Awaiting classification due to unclear treatment duration

Rivera 2010

Methods	Allocation: randomised, parallel, controlled trial Blinding: unclear Study duration: 7 months Location: Spain
Participants	Diagnosis: myofascial pain Total: n = 21
Interventions	**1. Acupuncture group**: (n = 11) **2. Lidocaine infiltrations**: (n = 10)
Outcomes	Pain intensity (VAS) Quality of life
Notes	This reference was waiting for translation to obtain clear information

Shen 2016

Methods	Allocation: randomised Blinding: not stated Study duration: unclear Location: Shangqiu, Henan, China
Participants	Diagnosis: idiopathic trigeminal neuralgia Total: n = 80 Sex: male 45; female 35 Age: mean ˜ 59.57 years; SD ˜ 6.27 years Length of illness: more than 4 months **Inclusion criteria**: not stated **Exclusion criteria**: not stated
Interventions	**1. Manual acupuncture group**: (n = 40) **2. Treatment as usual group** (carbamazepine tablets): (n = 40)
Outcomes	Pain intensity (VAS) Any pain-related outcome: no clinical response*, frequency of pain, duration of pain Specific adverse events
Notes	Awaiting classification due to unclear treatment duration *no clinical response: no improvement or even worse after treatment

Yue 2016

Methods	Allocation: randomised Blinding: not stated Study duration: not stated Location: Neimenggu, China
Participants	Diagnosis: diabeteic PN Total: n = 44 Sex: male 25; female 19 Age: mean ˜ 38.9 years; SD ˜ 8.2 years Length of illness: 5-25 years **Inclusion criteria**: not stated **Exclusion criteria**: not stated
Interventions	**1. Acupuncture + western medicine group**: (n = 22) **2. Western medicine group**: (n = 22)
Outcomes	Pain-related outcome: no clinical response*
Notes	Awaiting classification due to unclear treatment duration *no clinical response: no definition

CT: Computed Tomography; **EA**: Electric Acupuncture; **EMG**: Electromyography; **MRI**: Magnetic Resonance Imaging; n: number of participants; **NCS**: nerve conduction studies; **PN**: peripheral neuropathy; **RCT**: randomised controlled trial; **SD**: standard deviation; **TCM**: traditional Chinese medicine; **TENS**: Transcutaneous Electrical Nerve Stimulation; **VAS**: Visual Analogue Scale; **WHO**: World Health Organization

Characteristics of ongoing studies *[ordered by study ID]*

NCT01163682

Trial name or title	Acupuncture study for the prevention of taxane induced myalgias and neuropathy
Methods	Allocation: randomised Blinding: double blind (subject, caregiver, investigator) Estimated duration: December 2010-December 2015 Location: USA Length of follow-up: 16 weeks
Participants	Diagnosis: breast cancer Total: n = 50 Sex: female Age: > 21 years Length of illness: not stated

NCT01163682 *(Continued)*

	Inclusion criteria: age > 21 years; history of stage I-III breast cancer; scheduled to be receiving weekly adjuvant paclitaxel for 12 weeks; signed informed consent **Exclusion criteria**: previous treatment with acupuncture; diabetic neuropathy or other neurological conditions; inflammatory, metabolic or neuropathic arthropathies; current narcotic use; severe concomitant illnesses; severe coagulopathy or bleeding disorder; dermatological disease within the acupuncture area
Interventions	**1. Electroacupuncture group** (n = 25) **2. Sham group** (n = 25) Treatment duration: 12 weeks
Outcomes	Pain: difference in neuropathic pain between the 2 arms (measured by the mean Brief Pain Inventory-Short Form (BPI-SF)) Quality of life: FACT-Tax quality of life assessment Neurologic dysfunction (Grooved Pegboard test) Change in pro-inflammatory cytokines
Starting date	December 2010
Contact information	Dawn L. Hershman, Columbia University
Notes	No results have been published

NCT02104466

Trial name or title	Randomised controlled pilot trial of adjunct group acupuncture vs usual care among patients with painful diabetic neuropathy
Methods	Allocation: randomised Blinding: single blind (outcomes assessor) Estimated duration: March 2015-June 2016 Location: USA Length of follow-up: 12 weeks
Participants	Diagnosis: PDN Total: n = 60 Sex: both Age: > 18 years Length of illness: > 3 months **Inclusion criteria**: English or Spanish speaking; diagnosed with type 2 DM; distal lower limb pain present for ≥ 3 months; score of ≥ 4 on the 11-point Pain Intensity Numerical Rating Scale (PI-NRS) for the pain of diabetic PN ≥ 4 days/week before randomisation; pain characterised as burning, shooting, or stabbing in nature; ability to understand study procedures and willingness to comply with them for the entire length of the study; score of < 8 on the Semmes-Weinstein monofila-

NCT02104466 *(Continued)*

	ment test; stable use of pain control medications for PDN in the 1 month prior to screening (e.g. no change in prescription) or no use of pain control medications for PDN within the past month **Exclusion criteria**: substance abuse (as assessed by the Simple Screening Instrument for Substance Abuse); unstable medical condition (e.g. severe pulmonary disease, myocardial infarction, severe depressive symptoms); electrical therapy (e.g. TENS unit) or patch treatment (e.g. lidocaine or capsaicin) for PDN used within the past 2 weeks; acupuncture, moxibustion, cupping or herbal medicine for PDN used within the past 2 weeks; pregnancy, planning a pregnancy or breast-feeding; inability or unwillingness to comply with this study protocol, assessed prior to randomisation
Interventions	**1. TAU (treatment as usual) + acupuncture group** (n = 20): receive usual care with adjunctive acupuncture once/week for 12 weeks **2. TAU + acupuncture group** (n = 20): receive usual care with adjunctive acupuncture twice/week for 12 weeks **3. TAU group** (n = 20): receive usual care with no acupuncture Treatment duration: 12 weeks
Outcomes	Percentage of recruited participants retained, change from baseline in average weekly pain on the 11-point Pain Intensity Numerical Rating Scale (PI-NRS), Pain Qualities Assessment Scale, health-related quality of life, depressive symptoms using the Patient Health Questionnaire, participant rating of global improvement using the Patient Global Impression of Change scale, patient-centered symptom severity using the Measure Yourself Medical Outcome Profile, NIH PROMIS Sleep Disturbance Scale, Protective sensation of the feet using a 5.07 Semmes-Weinstein monofilament, patient satisfaction, use of medications
Starting date	March 2015
Contact information	Maria T Chao, chaom@ocim.ucsf.edu
Notes	No results have been published

NCT02553863

Trial name or title	A randomised controlled trial to assess the effectiveness and cost-effectiveness of acupuncture in the management of chemotherapy-induced peripheral neuropathy
Methods	Allocation: randomised Blinding: single blind (outcomes assessor) Estimated duration: September 2015-May 2017 Location: Hong Kong Length of follow-up: 20 weeks
Participants	Diagnosis: chemotherapy-induced PN Total: n = 98 Sex: both Age: child, adult, senior Length of illness: not stated **Inclusion criteria**: diagnosis of lung cancer receiving chemotherapy with curative intent, and breast or gynaecological cancer, head & neck and colorectal cancer stage I, II or III; currently receiv-

NCT02553863 *(Continued)*

	ing neurotoxic chemotherapy (taxanes, cisplatin, carboplatin, etc); reporting tingling in hands/feet and other indications of chemotherapy-induced PN after initiation of cancer treatments, confirmed to be indicative of chemotherapy-induced PN by a consultant; not using any medication for the prevention or treatment of chemotherapy-induced PN for the past 31 months; willing to participate and be randomised to one of the study groups; no previously established PN. **Exclusion criteria** needle phobia; low platelet count (< 50,000); comorbidity with a bleeding disorder; pregnancy; received acupuncture treatment in the past three months. In addition, the ipsilateral arm of participants who have undergone axillary dissection also excluded from needling as well as lymphoedematous limbs
Interventions	**1. Acupuncture group** (n = 49) **2. Standard care group** (n = 49) Treatment duration: 8 weeks
Outcomes	Pain measured using the Brief Pain Inventory, Grade of chemotherapy-induced PN, severity of neuropathy, quality of life measured using Functional assessment of cancer therapy (FACT/GOG-Ntx), sensory examination, measurement of costs, consumption of analgesics, motor nerve conduction
Starting date	September 2015
Contact information	Po Ling CHENG, +85227664132, irene.pl.cheng@polyu.edu.hk
Notes	No results have been published

NCT02831114

Trial name or title	Evaluating the effects of acupuncture in the treatment of taxane induces peripheral neuropathy (TIPN)
Methods	Allocation: randomised Blinding: open label Estimated duration: May 2016-December 2016 Location: USA Length of follow-up: 12 weeks
Participants	Diagnosis: taxane-induced PN Total: n = 18 Sex: female Age: > 18 years Length of illness: not stated **Inclusion criteria**: histologically confirmed primary invasive carcinoma of the breast (stage I, II, or III); completed active chemotherapeutic with taxane therapy (taxotere, Taxol, Abraxane) within the last 24 months; established diagnosis of motor and sensory neuropathy ≥ 2 according to the CTCAE v 4.03 scale in spite of previous treatment with Neurontin, Cymbalta and/or Lyrica; read, understand, and speak English

NCT02831114 *(Continued)*

	Exclusion criteria: currently undergoing active treatment with chemotherapy (not including TKI's or other targeted therapy); any acupuncture treatment for any indication within the 30 days of enrolment; cardiac pacemaker; deformities that interfere with accurate acupuncture point locations; local infection at or near the acupuncture site; pregnant or currently lactating; medical history of chronic alcohol use; mental incapacitation or significant emotional or psychological disorder
Interventions	**1. Acupuncture group** (n = 9) **2. Control group** (no intervention) (n = 9) Treatment duration: 12 weeks
Outcomes	Change in taxane-induced PN symptoms measured by the Patients' Global Impression of Change (PGIC) scale, Evaluate the mechanism of acupuncture as a treatment of taxane-induced PN through quantification of inflammatory biomarkers and circulation levels of mitochondrial DNA (mtDNA) Change in quality of life using the FACT/GOG-NTX questionnaire Evaluate if neuropathic mechanisms are contributing to pain measured by the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale Change in taxane-induced PN-related pain measured by the Brief Pain Inventory (BPI)
Starting date	May 2016
Contact information	Mark A O'Rourke, MORourke@ghs.org; Renee J LeClair, LeClairr@greenvillemed.sc.edu
Notes	No results have been published.

Shin 2011

Trial name or title	Electroacupuncture to treat painful diabetic neuropathy: study protocol for a three-armed, randomised, controlled pilot trial
Methods	Allocation: random numbers will be generated using a computerised random number generator through the stratified block randomisation method of the SAS package with a random block size of 3 prepared by a statistician who is blinded to this trial. Blinding: participants and the outcome assessors will be blinded to the type of acupuncture, and the data managers, statisticians and study monitors will be blinded to the allocation. Estimated duration: recruitment is expected to be completed from June 2012- July 2013 Location: Daejeon University Hospital in Daejeon, Korea Length of follow-up: 16 weeks
Participants	Diagnosis: PDN Total: n = 45 Sex: both Age: 18-75 years old

Shin 2011 *(Continued)*

	Length of illness: ≥ 6 months **Inclusion criteria**: men and women aged 18-75 years; diagnosis of type 1 or 2 DM; distal symmetric lower limb pain present for ≥ 6 months; ≥ 4 on the 11-point Pain Intensity Numerical Rating Scale (PI-NRS) for the pain of diabetic PN ≥ 4 days/week before the randomisation; ≥ 3 scores on the history and physical examination portion of the Korean version of the Michigan Neuropathy Screening Instrument (MNSI); ≥ 2 abnormalities on the following measures: (1) vibration perception by a 128 Hz tuning fork; (2) 10 g monofilament test; (3) ankle reflexes; stable use (variation of a major drug ≥ 25%) of pain control medications for PDN in the three months prior to screening or no use of pain control medications for PDN within the past month. **Exclusion criteria**: substance abuse or dependence; cardiovascular disorder (e.g. arrhythmia) or a pacemaker; neuropsychiatric conditions (e.g. epilepsy, depression or panic disorder); other diabetic microvascular complications (for example, diabetic nephropathy or diabetic retinopathy) within the past 3 months; HbA1c > 11%; change in antihyperglycemic medications in the 3 months prior to screening; diagnosis of diabetic foot ulcer; presence of severe pain other than that induced by PDN (for example, arthritis, back pain or headache); abnormal blood test (HbA1c, blood urea nitrogen, creatinine, thyroid-stimulating hormone, triiodothyronine, free thyroxine, vitamin B12) or urine test (proteinuria); neuropathic pain caused by a condition other than DM (for example, malignant disease, tarsal tunnel syndrome, neurothlipsis, vitamin B12 deficiency, hypothyroidism, neurotoxicity (e.g. lead, alcohol or smoking), medication (e.g. chemotherapy or isoniazid), transient ischaemic attack, stroke, multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, uraemic neuropathy, sub-acute combined spinal cord degeneration, phantom limb pain or atherosclerosis obliterans); known hypersensitivity reaction after acupuncture treatment or an inability to co-operate with the acupuncture procedure; electrical therapy or patch treatment (e.g. lidocaine or capsaicin) for PDN used within the past 2 weeks; acupuncture, moxibustion, cupping or herbal medicine for PDN used within the past 2 weeks; participation in other clinical trials within the past 3 months; pregnancy, planning a pregnancy or breast-feeding; unwillingness to comply with this study protocol
Interventions	**1. Electroacupuncture group** (n = 15) **2. Sham group** (n = 15) **3. Usual care group** (n = 15) Treatment duration: 8 weeks
Outcomes	Pain Intensity: PI-NRS; Quality of life: SF-MPQ, Sleep disturbance score, SF-36, Beck Depression Inventory; PGIC (patient global impression of change) Adverse events
Starting date	June 2012
Contact information	Sun-mi Choi, Korea Institute of Oriental Medicine; smchoi@kiom.re.kr
Notes	No results have been published

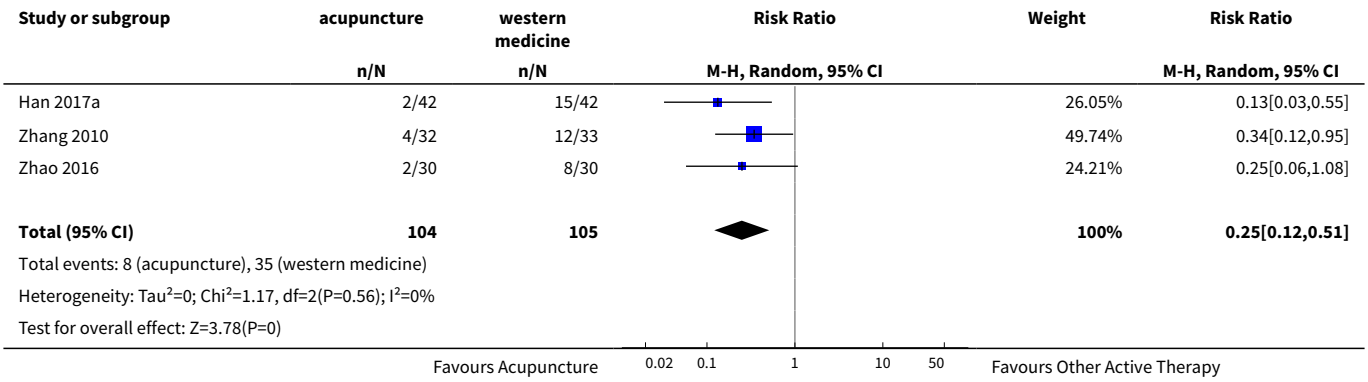
DM: diabetes mellitus; **MD**: mean difference; **MD**: mean difference; **n**: number; **PDN**: painful diabetic neuropathy; PN: peripheral neuropathy

DATA AND ANALYSES

Comparison 1. Acupuncture alone versus other active therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any pain-related outcomes: no clinical response - defined by original study	3	209	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.12, 0.51]

Analysis 1.1. Comparison 1 Acupuncture alone versus other active therapy, Outcome 1 Any pain-related outcomes: no clinical response - defined by original study.



ADDITIONAL TABLES

Table 1. Acupuncture points used in included studies

Acupuncture points used	Study ID
Taixi (KI3); Hegu (LI4); Taichong (LR3); Sanyinjiao (SP6); Zusanli (ST36)	Garrow 2014
Shenmai (B62); Zulinqi (GB41); Zhaohai (K6); Lieque (L7); Neiguan (P6); Houxi (SI3); Waiguan (SJ5); Gongsun (SP4)	Han 2017a; Zhao 2016
Feishu (BL13); Geshu (BL17); Feiyang (BL58); Zulinqi (GB41); Zhiyang (GV9); Shendao (GV11); Shenzhu (GV12); Dazhui (GV14); Taichong (LR3); Sanyinjiao (SP6); Xuehai (SP10); Tianshu (ST25); Zusanli (ST36); Xiangu (ST43)	Han 2017
The main points: Huantiao (GB30); Yanglingquan (GB34); Sanyinjiao (SP6); Zusanli (ST36); **The auxiliary points (selected 2-3from following)**: Shenshu (BL23); Kunlun (BL60); Guanyuan (CV4); Qihai (CV6); Huantiao (GB30); Taixi (K3); Taichong (LIV3); Pishu (PL20)	Wang 2016
The main points: Ganshu (BL18); Pishu (BL20); Shenshu (BL23); Yishu; Feishu (BL58); Zusanli (ST36); Sanyinjiao (SP6), Taibai (SP3); Zutonggu; Qihai (CV6); Guanyuan (CV4); Fenglong(ST40) and Yanglingquan (GB34); **The auxiliary points**: Jianyu (LI15); Quchi (LI11); Shousanli (LI10); Hegu (LI4); Biguan (ST31); Futu (ST32); Liangqiu (ST34); Xiangu (ST43) and Neiting (ST 44); **Added for blood stasis points**: Geshu (BL17) and Xuehai (SP10);	Zhang 2010

Table 1. Acupuncture points used in included studies *(Continued)*

Added for severe numbness of the hands and feet points: Bafeng(EX-LE10) and Baxie (EX-UE9).

Table 2. Scales in this review

Outcomes	Scales	Description of scales	Relevant Studies
Participant-reported pain intensity	Visual Analogue Scale (VAS)	The VAS is a visual analogue scale for pain intensity, in which 0 means no pain and 10 (or 100) means the worst pain ever experienced.	Garrow 2014; Han 2017
Quality of life	Short Form (36) Health Survey (SF-36)	The SF-36 is a 36-item, patient-reported survey of patient health and consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score, the more disability. The 8 sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. Summary scores for the SF-12, version 2 (SF-12v2) health status measure are based on scoring coefficients derived for version 1 of the SF-36. The higher score is better.	Garrow 2014;
	Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity (FACT/GOG-Ntx) questionnaire	The FACT/GOG-Ntx questionnaire is used to investigate patients' daily activities and evaluate the degree of neuropathy. The questionnaire includes 7 questions about physical well-being, 7 questions about social/family well-being, 6 questions about emotional well-being, 7 questions about functional well-being and 9 questions about additional concerns. Where in each question, 0 = not at all and 4 = very much, lower is better.	Han 2017

Table 3. Single study data (continuous data)

Acupuncture versus sham acupuncture

Outcome	Specific measurement	Study	Manual acupuncture group			Sham acupuncture group			Effect measure	Statistical test
			Mean	SD	Total	Mean	SD	Total	MD (95%CI)	P value
Pain intensity	VAS[a]	Garrow 2014	5.8	2.6	24	6.2	2.3	21	-0.40 (-1.83 to 1.03)	0.58
Quality of life	SF-36[b]: physical health score	Garrow 2014	31.9	9.2	24	32.1	9.8	21	-0.20 (-5.78 to 5.38)	0.94
	SF-36: mental health score		39.2	14	24	35.7	12.6	21	3.50 (-4.17 to 11.27)	0.38
	SF-36: bodily pain score		37.7	27.4	24	27.7	16.9	21	10.00 (-3.13 to 23.13)	0.14

Acupuncture + other active therapies versus other active therapies

Outcome	Specific measurement	Study	Acupuncture + other active therapies group			Other active therapies group			Effect measure	Statistical test
			Mean	SD	Total	Mean	SD	Total	MD (95%CI)	P value
Pain intensity	VAS	Han 2017	3.23	0.17	52	4.25	0.197	52	-1.02 (-1.09 to -0.95)	< 0.00001
Quality of life	FACT/the GOG-Ntx[c]	Han 2017	32.98	0.542	52	35.17	0.518	52	-2.19 (-2.39 to -1.99)	< 0.00001

MD: mean difference; **SD**: standard deviation

[a]VAS: Visual Analogue Scale (0-10, lower is better)

[b]SF-36: Short Form (36) Health Survey (0-100, higher is better)

[c]FACT/the GOG-Ntx: Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/ Neurotoxicity questionnaire (lower is better)

Table 4. Single study data (dichotomous data)

Acupuncture versus sham acupuncture

Outcome	Study	Manual acupuncture group	Sham acupuncture group	Effect measure	Statistical test

Table 4. Single study data (dichotomous data) *(Continued)*

		Events	Total	Events	Total	RR (95%CI)	NNTB	P value
Withdraw from trial due to any cause	Garrow 2014	4	28	10	31	0.44 (0.16 to 1.25)	NNTB = 6	0.53
Adverse events: any cases	Garrow 2014	1	28	2	31	0.55 (0.05 to 5.78)	NNTB = 34	0.62
Acupuncture + other active therapies versus other active therapies								
Outcome	**Study**	**Acupuncture + other active therapies group**		**Other active therapies group**		**Effect measure**		**Statistical test**
		Events	**Total**	**Events**	**Total**	**RR (95%CI)**	**NNT**	**P value**
Any pain-related outcomes: no clinical response	Wang 2016	4	30	10	30	0.40 (0.14 to 1.14)	NNTB = 5	0.09
Withdraw from trial due to any cause	Han 2017	3	52	3	52	1.00 (0.21 to 4.73)	NA	1.00

NA: not applicable; **NNTB**: number needed to treat for an additional beneficial outcome; **RR**: risk ratio

APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several recent changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for the inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that must be considered in this new review:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011b; Moore 2011c), back pain (Moore 2010b), and arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010); in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials of less than 12 weeks duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion of patients with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis to 30% in fibromyalgia (Moore 2009; Moore 2010c; Moore 2013b; Moore 2014a; Straube 2008; Sultan 2008). A Cochrane Review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010d; Moore 2014b).
5. Imputation methods such as last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. GRADE: assessing the evidence

Quality of the evidence

Two review authors (ZYJ, YY) independently rated the quality of the outcomes. We used the GRADE system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software (GRADEpro GDT 2015), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011b).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect;
2. Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
3. Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
4. Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Schünemann 2011b).

1. High: randomised trials; or double-upgraded observational studies.
2. Moderate: downgraded randomised trials; or upgraded observational studies.
3. Low: double-downgraded randomised trials; or observational studies.
4. Very low: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the quality level of a body of evidence are:

1. limitations in the design and implementation of available studies suggesting high likelihood of bias;
2. indirectness of evidence (indirect population, intervention, control, outcomes);

3. unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
4. imprecision of results (wide confidence intervals);
5. high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

1. large magnitude of effect;
2. all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
3. dose-response gradient.

We decreased the grade rating by one (- 1) or two (- 2) (up to a maximum of - 3 to 'very low') if we identified:

1. serious (- 1) or very serious (- 2) limitation to study quality;
2. important inconsistency (- 1);
3. some (- 1) or major (- 2) uncertainty about directness;
4. imprecise or sparse data (- 1);
5. high probability of reporting bias (- 1).

Appendix 3. Search strategy for CENTRAL (CRSO)

#1 MESH DESCRIPTOR Neuralgia EXPLODE ALL TREES

#2 MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES

#3 MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES

#4 (((pain* or discomfort*) adj5 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*))):TI,AB,KY

#5 (((neur* or nerv*) adj5 (compress* or damag*))):TI,AB,KY

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MESH DESCRIPTOR Acupuncture

#8 MESH DESCRIPTOR Acupuncture Therapy EXPLODE ALL TREES

#9 ((acupuncture or acupoint* or meridian*)):TI,AB,KY

#10 ((electroacupuncture or electro-acupuncture)):TI,AB,KY

#11 ((acupressure* or mox* or needling or acup* point*)):TI,AB,KY

#12 #7 OR #8 OR #9 OR #10 OR #11

#13 #6 AND #12

Appendix 4. Search strategy for MEDLINE via Ovid

1 exp Neuralgia/

2 exp Peripheral Nervous System Diseases/

3 exp Somatosensory Disorders/

4 ((pain* or discomfort*) adj5 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).tw.

5 ((neur* or nerv*) adj5 (compress* or damag*)).tw.

6 or/1-5 (199037)

7 Acupuncture/

8 exp Acupuncture Therapy/

9 (acupuncture or acupoint* or meridian*).tw.

10 (electroacupuncture or electro-acupuncture).tw.

11 (acupressure* or mox* or needling or acup* point*).tw.

12 or/7-11

13 6 and 12

14 randomized controlled trial.pt.

15 controlled clinical trial.pt.

16 randomized.ab.

17 placebo.ab.

18 drug therapy.fs.

19 randomly.ab.

20 trial.ab.

21 groups.ab.

22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23 exp animals/ not humans.sh.

24 22 not 23

25 13 and 24

Appendix 5. Search strategy for Embase via Ovid

1 exp Neuralgia/

2 exp Peripheral Nervous System Diseases/

3 exp Somatosensory Disorders/

4 ((pain* or discomfort*) adj5 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).tw.

5 ((neur* or nerv*) adj5 (compress* or damag*)).tw.

6 or/1-5

7 Acupuncture/

8 exp Acupuncture Therapy/

9 (acupuncture or acupoint* or meridian*).tw.

10 (electroacupuncture or electro-acupuncture).tw.

11 (acupressure* or mox* or needling or acup* point*).tw.

12 or/7-11

13 6 and 12

14 random$.tw.

15 factorial$.tw.

16 crossover$.tw.

17 cross over$.tw.

18 cross-over$.tw.

19 placebo$.tw.

20 (doubl$ adj blind$).tw.

21 (singl$ adj blind$).tw.

22 assign$.tw.

23 allocat$.tw.

24 volunteer$.tw.

25 Crossover Procedure/

26 double-blind procedure.tw.

27 Randomized Controlled Trial/

28 Single Blind Procedure/

29 or/14-28

30 (animal/ or nonhuman/) not human/

31 29 not 30

32 13 and 31

33 limit 32 to embase

Appendix 6. China National Knowledge Infrastructure (CNKI)

#1 Neuralgia*:ti,ab,kw

#2 Neurodynia*:ti,ab,kw

#3 Paroxysmal neuralgia*:ti,ab,kw

#4 Nerve pain*:ti,ab,kw

#5 Spontaneous pain*:ti,ab,kw

#6 Sciatic*:ti,ab,kw

#7 Sciatic neuritis*:ti,ab,kw

#8 Sciatica*:ti,ab,kw

#9 Causalgia*:ti,ab,kw

#10 Peripheral Nerve Disease*:ti,ab,kw

#11 Peripheral Nervous System Disease*:ti,ab,kw

#12 Peripheral Nervous System Disorder*:ti,ab,kw

#13 Peripheral Neuropathy:ti,ab,kw

#14 PNS Disease*:ti,ab,kw

#15 or/1-14

#16 Acupuncture:ti,ab,kw

#17 Needl*:ti,ab,kw

#18 Moxibustion*:ti,ab,kw

#19 or/16-18

#20 Randomized Controlled Trial:full text

#21 Controlled Clinical Trial:full text

#22 Random*:full text

#23 or/20-22

#24 and/15,19,23

Appendix 7. Chinese BioMedical Literature Database (CBM)

#1 MeSH:Neuralgia/explode all trees

#2 MeSH:Sciatica/explode all trees

#3 MeSH:Causalgia/explode all trees

#4 MeSH:Peripheral Nervous System Diseases/explode all trees

#5 Neuralgia*:ti,ab,kw

#6 Neurodynia*:ti,ab,kw

#7 Paroxysmal neuralgia*:ti,ab,kw

#8 Nerve pain*:ti,ab,kw

#9 Spontaneous pain*:ti,ab,kw

#10 Sciatic*:ti,ab,kw

#11 Sciatic neuritis*:ti,ab,kw

#12 Sciatica*:ti,ab,kw

#13 Causalgia*:ti,ab,kw

#14 Peripheral Nerve Disease*:ti,ab,kw

#15 Peripheral Nervous System Disease*:ti,ab,kw

#16 Peripheral Nervous System Disorder*:ti,ab,kw

#17 Peripheral Neuropathy:ti,ab,kw

#18 PNS Disease*:ti,ab,kw

#19 or/1-18

#20 MeSH:Acupuncture/explode all trees

#21 MeSH:Acupuncture Therapy/explode all trees

#22 MeSH:Needling Methods/explode all trees

#23 MeSH:Electroacupuncture/explode all trees

#24 MeSH:Needle Warming Therapy/explode all trees

#25 MeSH:Microwave Acupuncture/explode all trees

#26 MeSH:Specific Tissue Acupuncture/explode all trees

#27 MeSH:Specific Region Acupuncture/explode all trees

#28 MeSH:Manual Acupuncture/explode all trees

#29 MeSH:Air Acupuncture Therapy/explode all trees

#30 MeSH:Cutaneous Acupuncture/explode all trees

#31 MeSH:Laser Acupuncture/explode all trees

#32 MeSH:Fire-Needle Therapy/explode all trees

#33 MeSH:Electric Stimulation Therapy/explode all trees

#34 MeSH:Di-Needle Therapy/explode all trees

#35 MeSH:Pricking Blood Therapy/explode all trees

#36 MeSH:Long Needle Therapy/explode all trees

#37 MeSH:Flint Acupuncture/explode all trees

#38 Acupuncture:ti,ab,kw

#39 Needl*:ti,ab,kw

#40 Moxibustion*:ti,ab,kw

#40 or/20-39

#41 MeSH:Randomized Controlled Trial/explode all trees

#42 MeSH:Randomized Controlled Trial/publication type

#43 MeSH:Controlled Clinical Trial/explode all trees

#44 MeSH:Controlled Clinical Trial/publication type

#45 Random*:ti,ab,kw

#46 or/41-45

#47 and/19,40,46

Appendix 8. Wanfang Database

#1 Neuralgia*:ti,ab,kw

#2 Neurodynia*:ti,ab,kw

#3 Paroxysmal neuralgia*:ti,ab,kw

#4 Nerve pain*:ti,ab,kw

#5 Spontaneous pain*:ti,ab,kw

#6 Sciatic*:ti,ab,kw

#7 Sciatic neuritis*:ti,ab,kw

#8 Sciatica*:ti,ab,kw

#9 Causalgia*:ti,ab,kw

#10 Peripheral Nerve Disease*:ti,ab,kw

#11 Peripheral Nervous System Disease*:ti,ab,kw

#12 Peripheral Nervous System Disorder*:ti,ab,kw

#13 Peripheral Neuropathy:ti,ab,kw

#14 PNS Disease*:ti,ab,kw

#15 or/1-14

#16 Acupuncture:ti,ab,kw

#17 Needl*:ti,ab,kw

#18 Moxibustion*:ti,ab,kw

#19 or/16-18

#20 Randomized Controlled Trial:all fields

#21 Controlled Clinical Trial:all fields

#22 Random*:all fields

#23 or/20-22

#24 and/15,19,23

Appendix 9. Chongqing Weipu (VIP)

#1 Neuralgia*:ti,ab

#2 Neurodynia*:ti,ab

#3 Paroxysmal neuralgia*:ti,ab

#4 Nerve pain*:ti,ab

#5 Spontaneous pain*:ti,ab

#6 Sciatic*:ti,ab

#7 Sciatic neuritis*:ti,ab

#8 Sciatica*:ti,ab

#9 Causalgia*:ti,ab

#10 Peripheral Nerve Disease*:ti,ab

#11 Peripheral Nervous System Disease*:ti,ab

#12 Peripheral Nervous System Disorder*:ti,ab

#13 Peripheral Neuropathy:ti,ab

#14 PNS Disease*:ti,ab

#15 or/1-14

#16 Acupuncture:ti,ab

#17 Needl*:ti,ab

#18 Moxibustion*:ti,ab

#19 or/16-18

#20 Randomized Controlled Trial:any fields

#21 Controlled Clinical Trial:any fields

#22 Random*:any fields

#23 or/20-22

#24 and/15,19,23

WHAT'S NEW

Date	Event	Description
20 June 2019	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

Developing the protocol: ZYJ, KW, HSC, JX

Search: JX

Study screening: JZ, TYC

Data extraction: ZYJ, YY

Assessment of risk of bias: HSC, SML

Data analysis: HSC, ZYJ

Review writing: ZYJ, YY, SML

Final proof the manuscript: KW, JX

Update the review: KW, ZYJ

DECLARATIONS OF INTEREST

ZYJ: none known; ZYJ is an acupuncture physician and uses acupuncture in clinical work managing patients with various diseases.

KW: none known; KW is a clinical medical researcher.

HSC: none known; HSC is an acupuncture physician and uses acupuncture in clinical work managing patients with various diseases.

YY: none known; YY is a specialist anorectal surgeon and manages patients with anorectal diseases.

SML: none known; SML is an acupuncture physician and uses acupuncture in clinical work managing patients with various diseases.

JZ: none known; JZ is a specialist cardiothoracic surgeon and manages patients with cardiothoracic diseases.

TYC: none known; TYC is a specialist cardiothoracic surgeon and manages patients with cardiothoracic diseases.

JX: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Types of interventions

We intended to include studies with at least eight weeks of treatment, as opposed to eight weeks of study duration. This was not clearly expressed in the published protocol, hence we clarified this in the current full review. Due to this change, the originally planned cut-off time points for analysis (e.g. short-, medium-, and long-term) were no longer applicable, and were removed.

We added the fourth comparison "acupuncture combined with other active therapy versus other active therapy" in this section. This was not clearly stated in the published protocol other than one sentence ("acupuncture either given alone or in combination with other therapies"). Therefore, we clarified the fourth comparison in the current full review for consistency between sections.

2. Types of outcome measures

'Quality of life' was a planned outcome measure, but it was mistakenly omitted from the PICO section of the published protocol, even though it was listed as one of the seven 'Summary of findings' outcomes. We have rectified this error by adding 'Quality of life' to the outcome list.

3. Measures of treatment effect

We transferred the statement about the use of a random-effects model from 'Measures of treatment effect' to 'Data synthesis' section.

4. Data synthesis

In the protocol we stated that we planned to analyse data for each painful condition in three tiers. However, in light of the evolving methodology, we adopted the GRADE approach to assess the quality of the body of evidence for each important outcome in line with current Cochrane guidelines.

5. Subgroup analysis and investigation of heterogeneity

We deleted the second planned subgroup analysis on 'different treatment durations' as we included all studies with more than eight weeks treatment duration making the original planned analysis redundant.

NOTES

A restricted search in June 2019 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

*Acupuncture Therapy; Analgesics [therapeutic use]; Chronic Pain [*therapy]; Drugs, Chinese Herbal [therapeutic use]; Inositol [therapeutic use]; Neuralgia [*therapy]; Nimodipine [therapeutic use]; Pain Measurement; Quality of Life; Randomized Controlled Trials as Topic; Vitamin B 12 [analogs & derivatives] [therapeutic use]

MeSH check words

Adult; Humans; Middle Aged